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THE ENHANCED CARDIOVASCULAR FUNCTION WITH ENDURANCE TRAINING: THE MECHANISMS OF PRIMARY IMPORTANCE

by

Darren E. R. Warburton ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Faculty of Physical Education and Recreation

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "***The enhanced cardiovascular function with endurance training: The mechanisms of primary importance.***" submitted by Darren E.R. Warburton in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Dr. Robert C. Welsh

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Abstract

The purpose of this dissertation was to gain further knowledge regarding the mechanisms of cardiovascular adaptation brought about by physical training, the upper limits to physical performance and how this knowledge can be applied to other populations. The first investigation revealed that endurance-trained athletes make use of myocardial energy-conserving mechanisms (i.e., the Frank-Starling effect) throughout incremental to maximal exercise. This adaptation seems to be related to an increased capacity for diastolic filling. This investigation also demonstrated that postural position has a large impact on the relative contributions of heart rate, myocardial contractility, and the Frank-Starling mechanism to the increase in cardiac function during exercise conditions.

The second investigation presented in this dissertation evaluated the impact of different forms of aerobic training on cardiovascular function and its determinants. This investigation revealed that continuous and interval training resulted in a significant improvement in cardiovascular fitness, with little change in left ventricular dimensions. The primary adaptation occurred within the myocardium's ability to transport blood. A large portion of the increase in cardiovascular function was related to the training-induced increase in vascular volumes. The early expansion in vascular volume was associated with an enhanced responsiveness of long-term blood volume regulation mechanisms. Interval training resulted in similar improvements in cardiovascular function, with smaller changes in vascular volumes in comparison to continuous training.

Two investigations were conducted to evaluate the upper limits to human performance. These investigations revealed that significant alterations in vascular volumes and haematologic indices occur after prolonged strenuous exercise. These changes serve to limit human performance, but are of little concern to health status. These investigations also revealed that if electrolyte balance is maintained the potentially serious complications associated with prolonged strenuous exercise and electrolytes are unlikely to occur. These investigations also demonstrated that ultra-endurance events and/or training generally do not lead to myocardial electrical instability.

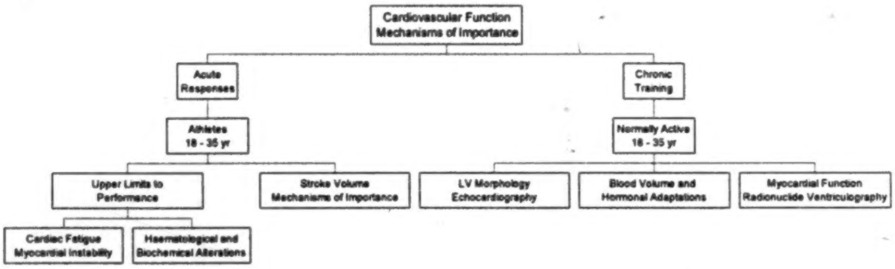
These findings set the ground work for future investigations, especially for the rehabilitation of patients with cardiovascular disease. Interval training may be more appropriate for patients with cardiovascular disease, where improvements in aerobic fitness are desired but changes in vascular volumes are not.

To Shannon Bredin.

For inspiring me to become a better person.

Preface

The outline of the dissertation entitled "**The enhanced cardiovascular function with endurance training: The mechanisms of primary importance**" is provided below. The primary purpose of this dissertation was to evaluate the mechanisms responsible for the improved cardiovascular performance after endurance training and apply this knowledge to other patient populations. Several investigations were conducted to evaluate the impact physical training has on cardiovascular function and its determinants. Given the recent interest of exercise physiologists and sport cardiologists alike in the role blood volume plays in cardiovascular function, particular interest was accorded to the impact aerobic training had on blood volume. A secondary purpose was to establish the upper limits to human performance by evaluating the effects of prolonged strenuous exercise on cardiovascular function. The final purpose of this dissertation was


Cardiovascular Function
Mechanisms of Importance
Acute Responses
Chronic Training
Athletes 18 - 35 yr
Normally Active 18 - 35 yr
Upper Limits to Performance
Stroke Volume Mechanisms of Importance
LV Morphology Echocardiography
Blood Volume and Hormonal Adaptations
Myocardial Function Radionuclide Ventriculography
Cardiac Fatigue Myocardial Instability
Haematological and Biochemical Alterations

to extrapolate the findings to the treatment of patients with cardiovascular disease.

In keeping with the aforementioned goals, this dissertation moves from the elite athlete model to sedentary men and the adaptations brought about by physical training. Chapter Two presents an overview of the literature regarding the adaptations to exercise training, especially the mechanisms utilized to derive high cardiac outputs during exercise conditions. Particular emphasis is given to the impact changes in the Frank-Starling mechanism have on cardiovascular performance. The relative role changes in preload (e.g., blood volume) have on cardiovascular function are also discussed.

Chapter Three presents an analysis of the mechanisms utilized by elite athletes to achieve their enhanced cardiovascular function during strenuous exercise. This chapter emphasizes the capacity of endurance-trained individuals to utilize the Frank-Starling mechanism during incremental exercise. This chapter also highlights the effects of changes in postural position on myocardial function and myocardial oxygen consumption.

Chapter Four covers three distinct areas including the effects of aerobic training on left ventricular morphology, blood volume and the hormones involved in blood volume regulation, and myocardial function. Particular interest was accorded to the impact that changes in vascular volumes have on cardiovascular performance.

The upper limits to human performance with regards to a series of haematological, biochemical and electro physiological parameters are discussed in Chapters Five and Six. These chapters highlight the impact that prolonged exercise has on physical performance and the potential for serious complications.

Chapter Seven provides an overview of the findings of the series of investigations reported in this dissertation. The impact of these findings are discussed with regards to physical performance and optimal living. The last chapter focuses on how this knowledge can be applied to patients with cardiovascular disease, especially congestive heart failure patients.

The overall intent of the dissertation is to provide the reader with a body of knowledge regarding the mechanisms of cardiovascular adaptation brought about by physical training, the upper limits to physical performance and how this knowledge can be applied to other populations. It is hoped that these objectives were achieved.

Appendices

The appendices provide a complete summary of techniques utilized in the completion of this investigation. Appendix A covers the calculations utilized to determine oxygen uptake using data obtained by open-circuit spirometry. Appendix B encompasses the calculations used to determine plasma volume and total blood volume via the Evans Blue dye dilution procedure. Appendix C contains the radioimmunoassay procedures utilized for the determination of atrial natriuretic peptide and angiotensin II. Appendix D covers the radioimmunoassay procedures used for the measurement of aldosterone. Appendix E includes an explanation of coulter counter blood counting procedures.

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SYMBOLS AND ABBREVIATIONS

SYMBOL	**DEFINITION**
a-$\bar{v}DO_2$	Arterio-venous (mixed) Oxygen Difference
BP	Blood Pressure
BV	Blood Volume
DBP	Diastolic Blood Pressure
EDV	End-diastolic Volume
ECG	Electrocardiogram
EF	Ejection Fraction
ESV	End-systolic Volume
FS	Fractional Shortening
Hct	Haematocrit
[Hb]	Haemoglobin Concentration
MAP	Mean Arterial Pressure
mmHg	Millimetres of Mercury
min	Minutes
PV	Plasma Volume
$\dot{Q}$	Cardiac Output
RBC	Red Blood Cell
RCV	Red Cell Volume

SYMBOL	**DEFINITION**
SBP	Systolic Blood Pressure
SBP/ESV	Systolic Blood Pressure to End-systolic Volume Ratio
SD	Standard Deviation
SV	Stroke Volume
sec	Seconds
$\dot{V}O_2$	Oxygen Consumption
$\dot{V}O_2max$	Maximal Aerobic Power

CHAPTER ONE

INTRODUCTION

Extensive research has been conducted regarding the central and peripheral adaptations that result from endurance training. Endurance athletes derive an enhanced cardiovascular function from their prolonged training including increases in: maximal cardiac output ($\dot{Q}$), maximal stroke volume (SV), maximal arterio-venous oxygen difference (a-$\bar{v}DO_2$) and maximal aerobic power ($\dot{V}O_2$max) (1). The relationship between these increases and the enhanced cardiovascular function of endurance athletes has been widely investigated.

Cardiac function is a key factor in the limitation of cardiovascular performance (1). Endurance training results in an increase in maximal $\dot{Q}$ through an increase in maximal SV, since maximal HR is either unchanged or slightly reduced after training (1, 3, 5, 6, 8, 10, 12). Stroke volume is affected by several factors including heart size, systemic vascular resistance, myocardial contractility, and venous return.

Controversy exists over what mechanisms lead to the enhanced cardiovascular function of endurance-trained athletes. Endurance athletes commonly exhibit increased left ventricular (LV) dimensions (6). Heart size may lead to an enhanced capacity for filling during exercise conditions, which will serve to augment SV (9). However, changes in LV morphology are commonly not observed after short-term training (23-25), despite significant changes in $\dot{V}O_2$max and cardiac function. Likewise, a reduction in systemic vascular resistance is not a pre-requisite for changes in $\dot{V}O_2$max and cardiac function after endurance training (23). Thus, although changes in heart size and systemic vascular resistance after training can augment SV and $\dot{Q}$, these adaptations are not essential for an improvement in $\dot{V}O_2$max and cardiac function (23).

Some investigators have revealed that endurance trained individuals have an increased systolic performance indicating an enhanced myocardial contractility which allows for the increase in SV after training (13). Whereas, others have shown that endurance-trained athletes are able to achieve greater SV during exercise conditions as a result of an increased use of the Frank-Starling mechanism (8, 9, 16, 23).

There is considerable debate over the impact of myocardial contractility and the Frank-Starling mechanism on the increased SV during exercise conditions. Some investigators have reported that both untrained and trained individuals reach the limits of the Frank-Starling mechanism during moderate levels of exercise (7). The trained individuals are thought to have a greater end-diastolic volume (EDV), which allows for an increased SV and $\dot{Q}$ during moderate and maximal exercise. However, the differences in EDV and SV are not believed to increase during strenuous exercise (7), since there is insufficient time for ventricular filling. Thus, during the later stages of vigorous exercise the increase in $\dot{Q}$ in both untrained and trained individuals is the result of an increased heart rate (tachycardia) and increased myocardial contractility.

However, other investigators have revealed that endurance-trained individuals actually have an enhanced capacity to utilize the Frank-Starling mechanism throughout incremental to maximal exercise leading to an increase in SV throughout incremental exercise (8, 9, 16, 19-22). This is thought to be the result of an increased capacity for ventricular filling, which is in part a passive response to an elevated blood volume (BV) (8, 9, 16, 19-22).

Given the impact of BV on ventricular filling and myocardial function, further evaluation of the role BV has on cardiovascular function is warranted. Very few researchers have examined the independent effect of an increased BV on each of these variables (14, 16, 20). Several investigators have shown that there is a high correlation between BV and $\dot{V}O_2$max (2, 8, 16, 17, 20) and it was demonstrated that a large portion of the enhanced cardiovascular function of endurance athletes is directly related to their larger BV (8, 11, 16, 20).

It is well established that unscrupulous coaches, athletes and practitioners have sought artificial means to improve athletic performance. The use of blood doping and recombinant erythropoeitin are two examples of attempts to improve endurance performance. It is generally concluded that the improvements in aerobic performance brought about by blood doping were the result of alterations in total body haemoglobin and red cell volume, leading to an enhancement in oxygen transport. However, changes in haemoglobin concentration and red cell volume are generally interrelated with changes in BV. It has recently been shown that volume loading via increases in SV and $\dot{Q}$ (independent of increases in red blood cells) has a potential ergogenic property (16). It is therefore important to understand the role BV plays in the enhanced cardiovascular function of endurance athletes and how BV may be manipulated to optimize cardiovascular performance.

The primary purpose of this dissertation, therefore, was to evaluate the mechanism(s) utilized by endurance trained individuals to increase their $\dot{Q}$ during exercise conditions. A secondary purpose was to examine the role BV plays in the enhanced cardiovascular function of endurance-trained individuals. If an expanded BV is important for optimal cardiovascular performance, then it would be advantageous for this volume expansion to be maintained. There is a series of hormones (i.e., angiotensin II, aldosterone, and atrial natriuretic peptide) involved in the long-term regulation of BV, which may be affected training-induced BV expansion. Therefore, another purpose of this investigation was to evaluate the role volume-regulatory hormones play in the induction and maintenance of training-induced BV expansion.

It has recently become apparent that repeated bouts of prolonged, strenuous exercise may result in a depressed myocardial function (4, 15, 18) and/or a haematological and biochemical alterations that limit performance and/or are potentially dangerous. Therefore, another purpose of this dissertation was to determine the upper limits of human performance in trained athletes in response to ultraendurance events.

The final purpose of this dissertation was to try to apply this knowledge to the treatment of patients with cardiovascular disease. The application of this knowledge to the rehabilitation of patients with congestive heart failure (who experience severe LV dysfunction in large part due to a chronic volume overload) was particularly attractive.

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CHAPTER TWO

REVIEW OF THE LITERATURE

Part One: The enhanced cardiovascular function of endurance athletes: What mechanisms do these individuals utilize to achieve their high levels of performance?

Part Two: The effects of different forms of endurance training on blood volume, hormones involved in volume regulation, and left ventricular morphology and function.

Part Three: Effects of prolonged strenuous exercise: What are the upper limits to physical performance?

Abstract

Objective: *Considerable debate exists regarding the mechanisms used to increase stroke volume and cardiac output during incremental exercise. Endurance-trained athletes have an increased capacity to utilize the Frank-Starling mechanism, which may due in part to their larger blood volume (BV). Blood volume and haemoglobin concentration ([Hb]) play important roles in oxygen transport. Manipulation of both BV and [Hb] can markedly affect systemic oxygen transport and* $\dot{V}O_2$*max. However, the impact of BV in oxygen transport and cardiac function is not well understood. Therefore, the primary objective of this review of literature is to examine the mechanisms these endurance-trained individuals use to achieve their high cardiac outputs during exercise and the role of BV in the enhanced cardiovascular function of endurance-trained athletes. Also, little is known about the impact that different forms of endurance training have on BV, hormones involved in BV regulation, and left ventricular (LV) morphology and function. Therefore, the secondary purpose of this review was to evaluate the impact of continuous and interval training on BV, hormones involved in volume regulation and LV morphology and function. The enhanced cardiovascular function of endurance-trained athletes has been associated with a series of health benefits. However, recent evidence indicates that prolonged strenuous exercise may place highly trained athletes at or near their limits for cardiovascular performance. Several potentially dangerous and/or fatal complications have been associated with ultraendurance events including LV dysfunction and/or haematological and biochemical complications. Therefore, the third purpose of this review was to evaluate the effects of prolonged strenuous exercise on LV function and/or several haematological and biochemical parameters.* ***Data Sources:*** *An extensive research of MEDLINE along with cross-referencing was conducted for this review. Articles were included on the basis of their relevancy to the purpose of this review.*

Study Selection: *This article critically reviews investigations of both a cross-sectional and longitudinal nature.* ***Data Extraction:*** *A systematic analysis of data relating to the purposes of the review was performed and a summary of the results was placed in written or tabular form.* ***Data Synthesis:*** *Blood volume affects numerous aspects of cardiovascular function, but exerts its effects primarily through increases in stroke volume and cardiac output (i.e. the Frank-Starling effect). Endurance training results in an enhanced BV, which is associated with concomitant increases in stroke volume, cardiac output and* $\dot{V}O_2max$ *and perhaps an attenuated pressure-volume regulating response. Ultraendurance events place endurance-trained individuals at or near the limits for aerobic performance. Several potentially dangerous complications may arise from "extreme exercise" including LV dysfunction, ventricular arrhythmia, and haematological and biochemical compromise.* ***Conclusion:*** *Blood volume plays a key role in the enhanced cardiovascular function of endurance athletes, such that endurance athletes may be at an optimum BV for aerobic performance. Ultraendurance events may be associated with several adverse outcomes, which at best serve to impair performance and at worst result in death.*

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1.0 Effects of Endurance Training on Stroke Volume

Endurance training produces a number of central and peripheral adaptations, which allow an individual to sustain higher aerobic work rates (7). Perhaps the most important of these adaptations is an improved cardiac function, so that the heart becomes more effective and efficient in its circulation of blood. This is primarily due to an increased SV (7, 38, 39, 159). The SV of endurance-trained athletes is significantly larger than their non-trained counterparts at rest and throughout incremental exercise (2, 5, 7, 29, 38, 39, 61, 73, 85, 106, 136, 154, 157-159) allowing a concomitant increase in maximal $\dot{Q}$ ($\dot{Q}$max) (2, 38, 39, 61, 85, 157, 159). Increases in SV are attributed to a combination of intra myocardial factors (i.e. heart size and myocardial contractility) and extra myocardial factors (i.e. BV and venous return) (7, 42, 75). There is contradictory evidence concerning the mechanism by which SV is most influenced.

2.0 Factors Affecting Stroke Volume

a) Left Ventricular Morphology

Numerous investigations have been conducted examining the effects of differing forms of physical training on cardiac dimensions as reviewed by Pelliccia (113). These investigations have generally shown that endurance training and perhaps resistance training results in morphological adaptations of the athletes' heart in response to the high demands of their exercise training regimes.

Cardiac enlargement was first observed in athletes using thoracic percussion and in autopsies (115). With the advent of echocardiography in the 1970's, physicians were able to detect a pattern to the myocardial morphologic adaptations resulting from various training regimes. Investigations using echocardiography have revealed that athletes (77, 106, 126, 145) and non-athletes who engage in short-term training (32, 37) may have increased cardiac dimensions. According to Maron (100) the left ventricular end-diastolic dimension, wall thickness and calculated left ventricular mass of highly trained athletes are approximately 10, 15 to 20, and 45% larger, respectively, compared with matched control subjects. It is also evident that cardiac morphological adaptations may occur within weeks or months after the initiation of strenuous training and these adaptations may be reversed in a similar fashion following the cessation of training (100). Several investigations have revealed that the extent of myocardial adaptations seen after training are dependent on the type and intensity of training (100, 113, 137). Endurance runners are characterized by an enlarged ventricular cavity and a slightly increased ventricular wall thickness (100, 106, 113-115, 137). Whereas, athletes who perform strength or isometric form of exercise generally have a normal ventricular cavity size and an increased left ventricular wall thickness (52, 113, 137).

Endurance trained athletes commonly exercise at high $\dot{Q}$, which is largely the result of an increased SV owing to an augmented venous return and decreased total peripheral resistance (38). Peronnet et al. (115) postulated that endurance training necessitates a larger left ventricular cavity dimension to cope with the increased venous return and decreased total peripheral resistance. Thus, endurance training results in a situation of chronic volume overload, leading to an increased end-diastolic wall stress (52). According to the Law of Laplace, the heart must adapt to keep to wall stress down. Hence, an increased end-diastolic wall stress is a stimulus for cardiac hypertrophy and may result in an enlarged ventricular chamber, which allows wall stress to be maintained at normal levels (8). This myocardial adaptation is commonly referred to as eccentric hypertrophy (i.e. replication of myocardial sarcomeres in series) (52). In endurance athletes the myocardial morphological adaptations are thought to enhance diastolic filling and lead to a larger SV (e.g. the Frank-Starling effect).

The myocardial morphologic adaptations seen in strength or resistance trained athletes are different in comparison to endurance trained athletes. In the strength or resistance trained athletes the cardiac morphologic adaptations seen are generally limited to left ventricular wall thickening with insignificant alterations in left ventricular cavity size (113). Proponents of the left ventricular wall thickening after resistance training believe that a pressure overload to the heart occurs as a result of an extreme elevation in systolic and diastolic blood pressures due to the mechanical compression of blood vessels by the contracting muscles and from an increased intrathoracic blood pressure during the Valsalva manouevre (93, 113). It is believed that the increased wall stress experienced by the myocardium results in concentric hypertrophy (i.e. replication of sarcomeres in parallel) leading to an increased wall thickness with little or no change in chamber size (52, 113). However, the increases in left ventricular wall thickness in resistance trained athletes may not be as significant as was once thought. Haykowsky and coworkers (70) have recently shown that myocardial wall stress is not significantly elevated during resistance training and may not be a suitable stimulus for concentric hypertrophy.

Differences in individuals' heart size may be due to their genetic make-up, their training or a combination of both (115, 158). The marked cardiac enlargement witnessed in highly trained endurance athletes may be attributed to exercising for prolonged periods of time at high $\dot{Q}$. However, some athletes may be genetically predisposed to cardiac hypertrophy, since former endurance athletes maintain elevated left ventricular cavity dimensions after becoming sedentary (8). As a result of their genetically enhanced myocardium these individuals may be naturally selected to endurance activities.

It is also unclear whether the typically large blood volume (BV) of endurance athletes has an effect on their myocardial morphologic adaptations. We (85) have recently postulated that athletes may have a genetic predisposition to a large BV. It is possible that the cardiac hypertrophy observed in endurance athletes may be partially related to the enlarged resting BV. However, this hypothesis requires further investigation?

b) Afterload

Afterload, the force required to overcome the resistance to the ejection of blood, is also affected by endurance training (7, 13, 14). Afterload varies directly with arterial blood pressure and therefore can be decreased via reductions in total peripheral resistance. Total peripheral resistance decreases as a function of endurance training and is associated with the increased SV and $\dot{V}O_2$max observed after training (7, 13, 14, 157). Clausen has reported an inverse relationship between total peripheral resistance and $\dot{V}O_2$max (13, 14). Blomqvist and Saltin (7) postulated that a "marked reduction in peripheral resistance enables the athlete to generate a cardiac output of up to 40 $l \cdot min^{-1}$ compared to 20 litres in the sedentary subject at similar arterial pressures during maximal exercise." Without adaptations in total peripheral resistance the arterial pressures would have to be twice as high to attain the same $\dot{Q}$ (7, 8).

The arterioles are the major resistance vessels of the vascular system (7) and adapt to physiological stress of exercise allowing total vascular resistance to be decreased (8, 86). Exactly how the arterioles adapt to meet the demands of exercise is debatable. It is likely that there is an increased mechanical distensibility, maximal size and total number of arterioles along with a modified control of sympathetic (alpha-adrenergic) vasoconstriction and local vasodilation (8, 86). Regardless, both animal and human research have revealed that endurance training results in a decreased arteriolar resistance, an enhanced blood flow and SV (86, 143).

c) Myocardial Contractility

Investigators have postulated that the enhanced cardiovascular function of endurance athletes, especially during maximal exercise, is a result of an augmented myocardial contractility (78). Myocardial contractility refers to the ability of the myocardium to change contraction vigour without altering end-diastolic fibre length (i.e. a positive inotropic effect). An enhanced myocardial contractility may be the result of augmented intrinsic contractile properties of the heart and/or an enhanced response to inotropic stimulation (via agents such as catecholamines) (8, 157).

Research indicates that cardiac performance is enhanced as a result of physical training in humans (8). However, it is often hard to differentiate whether the improved cardiac performance is due to an enhanced myocardial contractility or other training-induced adaptations. In animal models, an enhanced contractility has been demonstrated using isolated perfused heart and cardiac muscle preparations (8). Blomqvist (8) also noted that several adaptations with regards to contractile proteins or the systems related to myocardial calcium regulation are likely involved in the improved cardiac performance seen after endurance training.

Plasma catecholamines (i.e. norepinephrine and epinephrine) are released from the adrenal medulla and from the ends of the sympathetic postganglionic fibres in response to sympathetic stimulation (149). Catecholamines bind to β-adrenergic receptors on the plasma membrane of myocardial cells and are involved in the activation of the cyclic AMP pathway. This results in an increased number of slow calcium channels being opened during excitation of the myocardium. Thus, more calcium enters the cell, leading to a more forceful contraction and increased rate of contraction (146). Concurrently, the rate of relaxation of the myocardium is increased through the phosphorylation of the sarcoplasmic reticulum calcium channels (146).

There is a marked increase in circulating catecholamines during the latter stages of vigorous exercise (i.e. work rates above 50% $\dot{V}O_2$max) (62, 69). This suggests that myocardial contractility is enhanced during the latter stages of exercise, which along with the sympathetic stimulation of heart rate will increase $\dot{Q}$. An enhanced response to inotropic stimulation has also been observed in endurance athletes (74). Thus, endurance training may result in an enhanced sympathetic stimulation of the myocardium, reflected in an improved myocardial contractility.

d) Preload

Preload, the magnitude of ventricular filling before contraction, is also increased by endurance training (157). Increases in this diastolic volume will result in an increased stretch of the myocardial fibres. According to the Frank-Starling mechanism, this increased preload and resultant stretching will lead to a greater ejection of blood and thus a larger SV (61, 75, 153).

An increased preload is associated with a series of mechanisms including; posture, skeletal muscle contractions (i.e. the muscle pump), respiratory pump, venous sympathetic tone and BV. Gravity results in venous pooling in the extremities, leading to a decreased venous return and preload. Therefore, upright exercise is associated with a lower end-diastolic volume and SV (at the same relative intensity) in comparison to supine exercise (4, 5, 30, 119).

As exercise intensity increases, the contraction of the working skeletal muscles increase resulting in a compression of the capacitance vessels, thereby forcing the venous blood towards the right atrium (8). Similarly, the mechanical compression of intra-abdominal vessels during respiration will result in an increased mean circulatory filling pressure that is transmitted to the heart allowing the pressure gradient for venous return to be substantially increased (135). Concomitantly, during inspiration the intrathoracic pressure decreases resulting in a net transfer of venous blood from the thoracic cavity towards the heart (47). During expiration, the pressure differences are reversed and the veins are refilled. The net result is an increase in ventricular preload as respiration increases (as seen during exercise).

An increased sympathetic tone of venous smooth muscle will result in decreased diameter and compliance of the capacitance vessels, resulting in an increased venous pressure. This increased pressure will increase the pressure gradient for venous return allowing for an increased ventricular preload. Concurrently, an increased sympathetic activation of arteries and arterioles in inactive areas of the body redistributes blood to the skeletal muscle allowing for an enhanced venous return. Finally, an enhanced BV will lead to an increased preload simply by increasing the total amount of blood available for return.

It is important to understand that the myocardium is ultimately limited by venous return. As Smith et al. (135) wrote "sympathetic stimulation of the heart or of the peripheral circulation – or even both at the same time – can have only moderate effects on cardiac output." For instance, referring to Guyton's cardiac function and venous return curves we see that maximal sympathetic stimulation without any peripheral effects results in only a 15-20% increase in $\dot{Q}$ above the resting value (A to B). When sympathetic stimulation has both cardiac and peripheral effects the $\dot{Q}$ can increase twofold as a result of the simultaneous increase in venous return and the leftward shift of the cardiac function curve (C). To achieve the maximum $\dot{Q}$, sympathetic stimulation and local vasodilation must be at play. When local vasodilation is combined with sympathetic stimulation of the heart and the peripheral vasculature, exercise $\dot{Q}$ may increase more than four times baseline (D).

3.0 Mechanism of Primary Importance: Myocardial Contractility or Venous Return

Although an increased heart size and reduced afterload have been observed and can result in an improved SV, these factors are considered to have minimal impact on the improvements seen in SV as result of endurance training (76, 157-159).

There is less certainty about whether an enhanced myocardial contractility is the primary cause of an increased SV and $\dot{Q}$ during maximal exercise or whether an increased preload is of primary importance. For instance, several researchers have postulated that at low and moderate exercise intensities, the Frank-Starling mechanism is mainly responsible for increasing SV and thus $\dot{Q}$ in endurance-trained individuals (56). This occurs due to increased end-diastolic volume (EDV), and therefore an increased SV (due to the Frank-Starling effect). It has been reported that these differences in EDV and SV of endurance-trained athletes continue during moderate and maximal exercise, but do not increase (56).

It is commonly accepted that SV reaches a plateau at a submaximal work rate of approximately 40%$\dot{V}O_2$max (2). Researchers believe that this plateau occurs because tachycardia limits the time available for diastolic filling, and thus limits EDV in both trained and untrained individuals (56, 62, 73, 118). It is therefore hypothesised that increased myocardial contractility and tachycardia have more effect on increasing $\dot{Q}$ than the Frank-Starling mechanism in the later stages of vigorous exercise (56, 62, 78, 118).

However, according to Guyton and coworkers (135) in severe exercise heart rate may increase 2.5- to 3- fold in comparison to rest in normal individuals. Therefore, if SV is not maximal, $\dot{Q}$max will increase by only 2.5 to 3 times the normal. Athletes, however, experience a substantially greater increase in $\dot{Q}$ of up to 5-6 times the resting value (e.g. from a resting value of 5 $l \cdot min^{-1}$ to a $\dot{Q}$max in excess of 30 $l \cdot min^{-1}$) (154). Therefore, for $\dot{Q}$ to increase during vigorous exercise it is reasonable to argue that both, myocardial contractility and tachycardia and the Frank-Starling mechanisms are at play. As Smith et al. (135)) argued "if the change in heart rate and the increase in stroke volume are both maximal, then the cardiac output may increase 5-6 times the normal value" in exercising normal humans.

A lot of the research in this area is clouded by differences in measurement techniques and testing procedures. For instance, many investigations have used measurement procedures, which are not suitable for maximal exercise conditions as reviewed by Warburton et al. (151, 152). The results obtained using these procedures may not accurately reflect the actual changes during maximal exercise. Also, many of the early SV investigations reported control data in the supine position and then compared it to SV measures in the erect position. However, postural changes from the supine position to the upright position (as previously discussed) will result in a net reduction in central BV and a concomitant reduction in venous return and SV. Therefore, the increases in SV during exercise may be concealed by the postural changes (135).

Recent investigations and previously overlooked findings (33, 61, 85, 124, 129, 138, 154) indicate that endurance athletes may have an increased ability to utilise the Frank-Starling mechanism during maximal exercise. This increased ability is thought to be primarily due to an enhancement in ventricular filling, which is a passive response to an increased preload in endurance athletes (61, 85). Therefore, an increased SV, $\dot{Q}$ and $\dot{V}O_2$max, may be the result of an increased preload, along with an enhanced myocardial contractility, increased heart size and/or a reduced afterload.

4.0 What role does blood volume play?

a) Blood Volume, Preload and Cardiac Output

One of the mechanisms by which an enhanced preload is achieved is through an increased BV. An increased BV will result in a shift to the right of the vascular function curve (Figure 2.1) and an increase in mean circulatory filling pressure. For instance, a 15 percent increase in BV is thought to result in a doubling of the mean circulatory filling pressure (144). With a constant cardiac function this will result in a significantly increased SV and $\dot{Q}$, if heart rate is maintained.

b) Blood Volume Adaptation to Endurance Training

Blood volume is known to increase as a function of endurance training (10, 54, 84, 110). In fact, Convertino (23) reported that endurance-trained athletes have a 20-25% larger BV than their untrained counterparts. This finding is supported by the data summarized in Table 2.1, from a series of cross-sectional investigations reporting mean BV values for untrained and/or trained individuals (10, 12, 28, 34, 61, 68, 75, 80, 84, 85, 112, 116, 130, 142, 154, 161). This summary highlights some important findings: 1) the BV of endurance-trained athletes is significantly larger (20-30%) than that seen in non-trained counterparts and is not affected by gender and/or age (12, 16), 2) BV, when related to body mass or lean body mass, is slightly higher in males than in females, 3) an increased BV may account for a large portion of the difference in $\dot{V}O_2$max between untrained and trained individuals. Although few cross-sectional investigations report maximal values of SV, it is also apparent that BV may account for a large portion of the difference in maximal SV (SVmax) between trained and untrained individuals.

The values for BV given in Table 2.1 may be somewhat misleading. In fact, early studies using the carbon monoxide rebreathe method may have reported a large overestimation in BV. Sawka and coworkers (130) postulated that this may be due to the fact that carbon monoxide is distributed to all iron-porphyrin molecules including those in skeletal and heart muscle, which may result in a variable volume of distribution that is 2-20% larger than the red cell volume. This overestimation may be exacerbated in endurance athletes due to a larger extravascular volume of distribution of carbon monoxide. Thus, the carbon monoxide method may overestimate absolute volumes and the percent difference between the BV of untrained and trained individuals.

Although the Evans' blue dye tends to give more accurate estimates of BV, it too may lead to an overestimation of absolute BV. The injection of Evans' blue may slightly overestimate plasma volume (PV) due to a rapid disappearance of albumin into a small perivascular compartment (3, 120). To avoid this potential overestimation, multiple blood samples should be taken over a period of 60 min, which is not practical in most research situations. Also, a small amount of dye may be lost in the infusion, resulting in an overestimation of PV. However, this error should be consistent between untrained and trained individuals. Therefore, the percent difference in BV between trained athletes and their untrained counterparts should be accurate despite an overestimation of absolute BV.

Further analysis of the cross-sectional investigations that used carbon monoxide to predict BV revealed a mean difference of approximately 25% between the relative BV of untrained and trained males. Investigations using Evans' blue dye to determine BV reported a lower difference in relative BV (~19%) between untrained and trained males. Whereas, investigations using double radio labelling (i.e. iodine-labelled albumin (^{125}I) and radiochromate labelled erythrocytes (^{51}Cr) for measures of both PV and red cell volume (RCV) revealed an approximate difference in relative BV of 14% between trained and untrained males. A significant number of the investigations reviewed in Table 2.1 used carbon monoxide procedures. Therefore, the estimated mean difference of 20-30% between untrained and trained individuals may represent an overestimation of the actual difference in BV. A closer approximation for the difference in BV between untrained and trained individuals may be 15-20%. Further cross-sectional research, using radio tracer techniques, is therefore needed to determine the average difference in BV between trained athletes and their sedentary counterparts.

A summary of the findings from a series of longitudinal investigations (12, 23, 27, 46, 57, 63-66, 92, 104, 105, 121, 122, 125, 133, 140) presented in Table 2.2 reveals that the amount of BV expansion resulting from training in men and women approximates 6% (across all investigations). Across all investigations, the average relative BV values for men increase from 72 $mL \cdot kg^{-1}$ before training to 76 $mL \cdot kg^{-1}$ after training. Whereas, the average relative BV values reported for women increase from 67 $mL \cdot kg^{-1}$ to 73 $mL \cdot kg^{-1}$. This is substantially lower than the percent difference in BV reported in cross-sectional investigations and indicates that short-term training is not sufficient to elicit an increase in BV similar to that of chronic endurance training. This is supported by Convertino (16) who postulated that the "hypervolemia induced by endurance exercise training is limited by such factors as initial fitness levels, duration of previous exposure to exercise training, or genetic components." A possible explanation for this discrepancy was proposed recently by Krip et al (85). They speculated that endurance-trained athletes are genetically endowed with a high BV, which provides them with an augmented SV and $\dot{Q}$, and hence a high $\dot{V}O_2max$. Endurance training simply tops up this genetically endowed high BV. Further research is needed to support this contention.

Hypervolemia reaches a plateau after one week of training (16). Short-term exercise-induced increases in BV are almost entirely due to an increase in PV and not RCV (16, 19, 20, 63, 64, 66, 67). There seems to be an overshoot of PV expansion early into intense training (10-12%) (20, 54) and PV then plateaus at four weeks of training

(16, 65) to become approximately 6-9% larger. Red blood cell volume will generally begin to increase after four weeks of training allowing the increase in BV to be more evenly distributed between increases in PV and RCV (1, 16, 17, 23, 122). It is important to realize however that some investigators have found no significant increase in BV, PV or RCV as result of prolonged training (133, 140). The reasons for these discrepancies are unclear, but may be related to differences in: participant population, training regimes, environmental conditions and/or the season in which the research was conducted (133). Further research into the role each of these factors plays on training-induced hypervolemia is warranted.

The rates at which increases in BV are achieved are dependent on the frequency, intensity and duration of the training protocol (Table 2.2). Exercise intensity is the major stimulus for increases for training-induced PV expansion (44, 66), since significant increases in BV are seen as a result of high intensity, short-term training (66, 125) and significant improvements in PV and BV can be achieved after a single bout of exercise (54). The magnitude of PV expansion is also closely related to the duration of each exercise bout (44). There is a direct correlation between the magnitude of BV expansion and exercise duration regardless of intensity and frequency (using the mean data reported in Table 2.2 excluding two outliers (121, 133)) (ΔBV (mL) = 2.89 + 0.07(Exercise Duration (min)), $r = 0.59$, $p < 0.05$).

The increase generally seen in BV as a result of endurance training is 300-500 mL (Table 2.2). Also, heat acclimation will result in a significant improvement in PV which is essential for heat tolerance (20). Heat acclimation alone produces hypervolemia to a lesser degree than exercise (20), however, the combination of exercise and heat acclimation results in a further increase in BV than that caused by training alone (44).

Blood volume has been shown to decrease with age in sedentary men and women (31, 112, 142) as a result of reductions in both PV and RCV. However, high levels of physical activity may prevent the age-related declines in BV and $\dot{V}O_2$max (112, 142).

The maintenance of a chronically expanded BV provides a series of cardiovascular and thermoregulatory benefits (16). Thermoregulatory advantages include an increased sweat rate and evaporative cooling during exercise, which minimise the increases in core body temperature during exercise (16). Cardiovascular advantages are thought to include a reduced heart rate (16, 19, 20, 22, 160), an increased SV (27, 61, 85, 154), and an increased $\dot{Q}$ (61, 85, 154) during submaximal and maximal exercise.

The majority of these investigations used a continuous training protocol at a submaximal intensity for a short-term (i.e. less than 6 weeks). Therefore, further investigations examining the effects of prolonged continuous aerobic training are needed to discern whether or not the BV differences observed in cross-sectional investigations (i.e. 15 to 20%) may be achieved. Also, many of these investigations have not monitored the alterations in BV on a week by week basis. It would be important to get an understanding of the weekly adaptations in BV that take place as a result of prolonged aerobic training.

Interval training, intermittent exercise with high intensity (90% to 120% of $\dot{V}O_2$max) work phases with rest phases (0 to 40% of $\dot{V}O_2$max), is a common method to improve aerobic fitness. However, little is known about the effects of prolonged interval training on BV and cardiac function. According to this review of the literature, the early increases in BV are directly related to the intensity of the exercise. However, the overall changes in BV are directly related to the duration of the exercise. The duration of exercise training is generally less during interval training in comparison to continuous training. Therefore, the potential exists for BV to be augmented to a greater extent by continuous training. To the best of my knowledge no investigation has examined the effects of prolonged interval training (i.e. training over 6 weeks) on BV and cardiac function. This is an area worth investigating, since it may give a clearer picture of the impact intensity and duration have on alterations in BV, aerobic fitness and left ventricular morphology and function.

5.0 Blood Volume, Haemoglobin Concentration and Oxygen Transport

Systemic oxygen transport is calculated as arterial oxygen content (CaO_2) multiplied by $\dot{Q}$ (59, 60). Therefore, both BV and [Hb] are interrelated and play key roles in the amount of oxygen transported to the tissues. A change in BV affects ventricular preload (via the Frank-Starling effect) and may alter SV and $\dot{Q}$, while a change in [Hb] will bring about a change in CaO_2, both of which will impact oxygen transport (59, 60). Hence, alterations in BV can influence both cardiac function and $\dot{V}O_2$max.

6.0 Blood Volume and Maximal Aerobic Power

Original investigations of the effects of manipulations in BV and [Hb] generally concluded that the latter (through alterations in total body Hb) plays the dominant role in the determination of $\dot{V}O_2$max (60, 79, 80). For instance, Kanstrup and Ekblom (80) reported that the effects of hypervolemia are dependent on total body Hb and the resultant [Hb]. An increase in $\dot{V}O_2$max and endurance performance can be achieved when hypervolemia is associated with an elevated [Hb]. However, when hypervolemia is associated with a reduced [Hb], $\dot{V}O_2$max and endurance performance are unchanged and/or reduced. This highlights the large importance of total body Hb for the determination of $\dot{V}O_2$max. Recent investigators, however, have shown that $\dot{V}O_2$max can be increased as result of BV expansion independent of changes in red blood cells (hypervolemic anaemia) in untrained individuals (28, 85). Therefore, when considering changes in [Hb] consideration must be given to the changes in BV. It is clear that BV plays a greater role in the determination of $\dot{V}O_2$max than was once thought.

An analysis of the relationship between BV and $\dot{V}O_2$max from mean values reported in the literature (taken from Table 2.1 and Table 2.2) reveals that there is a direct relationship between BV and $\dot{V}O_2$max (Figure 2.2). This relationship is supported by several researchers (16, 61, 85, 98, 105, 112, 142, 154, 161) and is contrary to researchers who contend that aerobic power is not related to vascular volumes (130, 133, 162). However, the impact of BV on $\dot{V}O_2$max is not well understood and requires further investigation.

7.0 Effects of Acute Blood Volume Expansion on Maximal Aerobic Power

a) Blood Doping and Maximal Aerobic Power

Numerous researchers have investigated the effects of artificially increased BV on $\dot{V}O_2$max. As reviewed by Gledhill (58-60) these studies have predominantly involved the re-infusion of whole blood (11, 139) or packed erythrocytes (40, 41). These investigators have generally shown that the infusion of red blood cells or re-infusion of whole blood (hypervolemic erythrocythemia) leads to increases in CaO_2, and therefore an increase in $\dot{V}O_2$max and endurance performance (40, 41). However, these investigations have not shown the actual effect an increased BV has on $\dot{V}O_2$max, since the increased oxygen carrying capacity of the blood (brought about by the increased [Hb]) could cause the observed increases in $\dot{V}O_2$max. Therefore, researchers have tried to increase BV, without changing RCV or total Hb, to independently study the effects of BV expansion.

b) Plasma Volume Expansion and Maximal Aerobic Power

Plasma volume expansion, as result of endurance training or through the use of artificial volume expanders, presents an opportunity to investigate the independent effects of BV expansion on $\dot{V}O_2$max. Increases in PV, as a result of training or acute volume expansion, can take place without concomitant increases in RCV, thereby resulting in a decreased [Hb] (hypervolemic anaemia). This could impair $\dot{V}O_2$max, since the working muscles may not have sufficient oxygen to perform the necessary work. However, PV expansion (especially after prolonged training) may be associated with an increased RCV and total Hb, such that [Hb] is not reduced. This condition is referred to as hypervolemia normocythemia (59). In this situation, aerobic performance is generally not adversely affected (59).

Several investigators have examined the effects of increases in PV and decreases in [Hb], due to either endurance training (20, 63) or acutely induced PV expansion (27, 28, 75, 79, 80, 82, 85, 154) (Table 2.3). Considerable controversy has arisen over whether PV expansion will lead to an increased $\dot{V}O_2$max.

Several investigators have reported that PV expansion of 500-700 mL has little effect on $\dot{V}O_2$max despite an 8-11% decrease in the oxygen-carrying capacity of blood (28, 63, 79, 80, 82, 154). The consensus of these researchers is that SV and $\dot{Q}$ increase due to the enhanced preload (ie. the Frank-Starling effect) and possibly a reduced afterload (due to the lower viscosity of the PV expanders). Therefore, reductions in arterial oxygen-carrying capacity are compensated by an increased blood flow allowing $\dot{V}O_2$max to remain unchanged. It is postulated that the total amount of Hb is of utmost importance for the maintenance of $\dot{V}O_2$max (81). However, these results also highlighted the role BV plays in oxygen transport and in the determination of $\dot{V}O_2$max, since a reduced [Hb] did not result in a reduced $\dot{V}O_2$max via compensations in SV and $\dot{Q}$ (153).

The absolute role that BV plays in the determination of $\dot{V}O_2$max is not straightforward. However, if BV is of relatively little importance to $\dot{V}O_2$max, PV expansion would not result in an improvement in $\dot{V}O_2$max. Several investigators contend that if the hemodilution effects of PV expansion are sufficiently offset by increases in SV and $\dot{Q}$, an increased $\dot{V}O_2$max may be achieved (18, 27, 28, 85) (Table 2.3). These researchers believe that if the increase in SV and $\dot{Q}$ is proportionally greater than the resultant hemodilution caused by PV expansion, $\dot{V}O_2$max may increase. This finding however only seems to be possible in untrained participants, since further BV expansion in endurance-trained athletes fails to result in any further improvements in $\dot{V}O_2$max (27, 75, 154).

Some researchers have concluded that a large portion of the difference in $\dot{V}O_2$max between trained and untrained individuals is due to the higher BV of the endurance-trained athletes (61, 68, 85). There also appears to be an optimal PV expansion for improvements in $\dot{V}O_2$max. As illustrated in Table 2.3, untrained individuals may increase SV and $\dot{V}O_2$max in response to an acute PV expansion of up to 400-500 mL (27, 75, 85). However, a PV expansion of greater than this volume does not result in any further improvements in cardiovascular function in untrained individuals (27, 75). The findings of these investigations give further indication that there is a fine balance between the amount of hemodilution and increases in SV as a result of PV expansion leading to an enhanced $\dot{V}O_2$max. If this optimal level of PV is exceeded, an increased $\dot{V}O_2$max will not be achieved and $\dot{V}O_2$max may remain unchanged or be reduced. Endurance trained athletes seem to be at an optimum BV for aerobic performance, since further PV expansion does not result in any further improvements in $\dot{V}O_2$max (Table 2.3).

The discrepancies between investigations shown in Table 2.3 may be resolved by examining the fitness levels of the participants and the volumes of PV infused. For instance, the majority of the investigations reporting no change in $\dot{V}O_2$max as a result of

PV expansion examined moderately trained or trained participants. Warburton (153) speculated that a significant increase in $\dot{V}O_2$max can be achieved via a 300-500 mL increase in PV in untrained subjects (with a relative $\dot{V}O_2$max of approximately 45 $mL \cdot kg^{-1} \cdot min^{-1}$). This may be in large part due to the untrained individuals' sub-optimal BV, whereas endurance athletes may be at an optimal BV for aerobic performance. It is understandable that acute PV expansion will not result in further improvements in aerobic performance in endurance athletes. Also, it appears that a volume expansion greater than 500 mL does not result in significant improvements in $\dot{V}O_2$max in untrained or moderately trained individuals.

8.0 Endurance Athletes and Diastolic Reserve

The optimum level of PV expansion has primarily been observed in untrained individuals and most likely represents the balance between hemodilution and improvements in SV. However, in endurance-trained athletes the minor changes in SV, $\dot{Q}$ and $\dot{V}O_2$max may be related to another mechanism. For instance, there may be a diastolic reserve capacity, which is encroached upon and/or exceeded as a result of PV expansion. The elevated BV of endurance athletes may place their LV at or near its capacity of their heart to utilize the extra volume. Whereas, untrained athletes may have a substantially larger reserve to utilize the extra volume.

This may seem paradoxical to research which indicates that endurance athletes have a significantly greater ventricular compliance and distensibility in comparison to their non-trained counterparts (87, 88). Levine (87) stated that athletes operate "on the steep portion of their Starling curve, with nearly twice the change in stroke volume for a change in filling pressure." Levine and coworkers (87, 88) postulated that this adaptation is advantageous during exercise allowing for high $\dot{Q}$max.

Blomqvist and Saltin (7) also speculated that endurance training may alter ventricular compliance by modifying right/left pericardial interactions, with the result being an increased diastolic reserve capacity. With an increase in BV, the ventricular preload seen by the heart is increased such that the transmural diastolic pressure is increased, which produces an increase in EDV. This is evident by the significantly greater

SV of endurance-trained athletes in comparison to untrained individuals. It would therefore be reasonable to assume that athletes would be better able to take advantage of additional BV. However, given the research using acute PV expansion in athletes (Table 2.3) (27, 154) it would seem that athletes cannot take further advantage of the extra BV.

The results of Coyle et al. (27), Hopper et al. (75), and Warburton et al. (154) infer that there may be an optimal diastolic reserve capacity beyond which point no further increases in SV can occur. The athletes in the investigation of Warburton et al. (154) had a large BV and consequently their diastolic reserve capacity was likely already encroached upon. Therefore, the large increases in SV and $\dot{V}O_2$max following PV expansion in untrained participants (27, 28, 85) were most likely not observed in endurance-trained athletes because of differences diastolic reserve. Thus, the elevated BV usually seen in endurance-trained athletes is at or near the optimum level for cardiovascular performance, any further increases in this volume may have no beneficial effects.

Hence, two possible outcomes of acute PV expansion exist: 1) optimum BV expansion, which sufficiently offsets the hemodilution effects of PV expansion, and 2) optimal diastolic reserve after which no further increases in SV and $\dot{Q}$ can be achieved. For untrained subjects, BV expansion relative to hemodilution seems to be of utmost importance for improvements in cardiac function and $\dot{V}O_2$max. Whereas, in endurance-trained athletes optimizing BV relative to individual diastolic reserve capacities seems to be of greater importance for improving cardiovascular function and $\dot{V}O_2$max.

9.0 Blood Volume and Cardiac Function

As previously outlined, endurance athletes display significantly larger BV and SV than their non-trained counterparts. What effect this augmented BV has on endurance athletes' cardiac function is not well understood? An expansion of BV may result in an increased preload augmenting the velocity of the rapid filling phase during diastole (26) and may lead to greater ventricular stretch according to the Frank-Starling mechanism, resulting in an increased SV. Several other cardiovascular adjustments may also assist the effects of an elevated BV on diastolic filling and $\dot{Q}$. For instance, the actions of the muscle pump, the actions of the respiratory pump, and decreases in peripheral resistance may all assist in the utilization of the elevated BV to further augment preload and therefore cardiac function (85, 157). These are all areas worthwhile of further investigation.

Coincident with an expanded BV, endurance athletes possess increased left ventricular cavity dimensions (52), an enhanced myocardial compliance (87), an augmented elastic recoil and increased negative left ventricular pressure (103). These adaptations all serve to enhance diastolic filling and therefore may allow endurance athletes to make greater use of the Frank-Starling mechanism during exercise (61, 85). What role BV expansion plays in each of these myocardial adaptations is unclear and requires further investigation. It is clear that the output of the myocardium may be improved as a result of BV expansion. Hopper et al. (75) postulated that approximately one-half of the difference in SV between trained and untrained participants is due to the sub-optimal BV of the untrained individuals.

10.0 Blood Volume, Endurance Training and the Volume-regulating Hormones

If an expanded BV as a result of training is of importance for an increased $\dot{V}O_2$max and an enhanced cardiovascular function, it would be beneficial for this expansion to be maintained for prolonged periods of time. Several investigators have postulated that an increased BV is the result of increased plasma protein content (19, 20, 54, 55). However, with an increase in protein content and vascular volume, intravascular pressures will increase, which would lead one to believe that volume/pressure regulatory mechanisms (i.e. the renin-angiotensin-aldosterone, atrial natriuretic peptide, and vasopressin systems) would try to lower the BV to normovolemic conditions (23, 55). However, the maintenance of a chronically expanded BV as result of endurance training has been well documented (16, 61, 85). Thus, a compensatory mechanism or mechanisms must be at play allowing an expanded BV to be maintained over a training regimen.

Plasma volume tends to decrease as exercise duration increases. Therefore, to prevent cardiovascular compromise, vascular volumes must be maintained. Two mechanisms occur during exercise to prevent further loss of PV; 1) a redistribution of blood flow from the splanchnic and renal circulation, to the skin and the working muscles and, 2) the release of a series of volume-regulating hormones (44).

a) Renin-Angiotensin-Aldosterone Hormone Systems

Renin is an enzyme released from the juxtaglomerular apparatus of the kidneys in response to a decrease in arterial blood pressure sensed by the intra-renal baroreceptors. Renin is involved in the conversion of angiotensinogen (synthesized by the liver) to angiotensin I (149). Angiotensin I is then converted by an enzyme in the lung to angiotensin II (149). Angiotensin II acts on specific receptors of target organs and stimulates peripheral vasoconstriction and the release of aldosterone from the adrenal cortex (43) (Figure 2.3). Angiotensin II, therefore, serves to modulate arterial blood pressure (43). Angiotensin II may also increase the stimulus for thirst (149) and is a direct inhibitor of renin secretion (negative feed-back system) (43).

The major determinant of tubular sodium reabsorption is aldosterone. Aldosterone is a released from the adrenal cortex in response to decreased levels of sodium or increased levels of angiotensin II, potassium and adrenocorticoptic hormone (149). The circulation of aldosterone is associated with increased sodium reabsorption and potassium excretion via the promotion of the activity of the sodium/potassium pump in the distal tubular cells of the kidney (43) leading to a passive reabsorption of water (47). Thus, the renin-angiotensin-aldosterone systems are involved in both water and sodium conservation.

b) Anti-diuretic Hormone (Arginine Vasopressin)

The major determinant of water reabsorption in the kidneys is the anti-diuretic hormone (arginine vasopressin) secreted by the posterior pituitary (neurohypophysis) in response to increased extracellular osmolarity (e.g., increased plasma sodium concentration). Vasopressin's main function is to promote solute-free water reabsorption from the collecting ducts of the kidney (47, 147) in order to maintain body fluid (19). Angiotensin II stimulates the release of vasopressin (132, 148) and may play a role in the regulation of vasopressin during exercise (147).

c) Atrial Natriuretic Peptide

Atrial natriuretic factor or peptide (ANP) may also play a role in sodium reabsorption and fluid homeostasis. Atrial natriuretic factor is secreted by the atria in response to an increase atrial pressure and distension (51). Atrial natriuretic factor is thought to exert its effect on the kidneys by inhibiting sodium reabsorption and therefore opposes the renin-angiotensin-aldosterone hormonal system. Atrial natriuretic factor may also affect renal water excretion by inhibiting the release of vasopressin (51).

d) Hormonal Responses to Exercise

Several investigations have observed increased plasma levels of renin, angiotensin, aldosterone and vasopressin during exercise (19, 21, 22, 25). As reviewed by Wade and Freund (149) plasma renin activity is increased in response to work rates above 70% $\dot{V}O_2$max and both plasma renin activity and angiotensin II levels increase 5- to 10-fold in response to maximal exercise. Exercise intensity and duration also seem to affect the response of the renin-angiotensin system. Wade and Claybaugh (148) revealed that elevation of plasma renin activity was linearly related to work intensity. Also, the duration of the exercise bout seemed to affect plasma renin activity since 20 min of submaximal exercise at 35% heart rate maximum failed to increase plasma renin activity, whereas after 60 min of exercise at the same exercise intensity plasma renin activity was increased.

Maximal exercise results in a 2- to 5-fold increase in plasma aldosterone levels (149). The duration of exercise seems to play a key role in the aldosterone response to exercise. Prolonged submaximal exercise may result in greater plasma levels of aldosterone than those observed after maximal exercise (45, 149, 150). Unlike the other hormones, elevated aldosterone levels remain hours after the cessation of exercise (25, 149).

The typical renin-angiotensin-aldosterone system response to exercise is illustrated in Figure 2.4. Exercise leads to an increase in sympathetic tone of the vascular bed and catecholamine release resulting in a stimulation of the β-adrenoreceptors on the juxtaglomerular cells of the kidneys. Renal hypoperfusion and stimulation of the renin-angiotensin system will occur as a result of vasoconstriction of the glomerular afferent arteriole and the redistribution of blood flow to the working muscles. With a decrease in hepatic and renal blood flow (128, 148) the metabolic clearance of renin will be reduced resulting in a further stimulation of the renin-angiotensin system (43).

Vasopressin is similarly increased as a result of exercise in response to an increased sympathetic activity, sodium loss, decreased plasma volume and increased osmolality (47, 149). According to Wade and Freund (149) the threshold for vasopressin release is work rates greater than 70% $\dot{V}O_2$max and the longer the duration of the event the greater the plasma levels of vasopressin. Wade and Claybaugh (148) revealed that the exercise-induced rise in plasma vasopressin levels was directly related to the work intensity and was dependent on the work duration. At an exercise intensity of 70% $\dot{V}O_2$max for 20 min there was no significant change in plasma vasopressin levels, however, after 60 min at the same intensity plasma vasopressin levels were significantly increased.

During low to moderate exercise intensities, ANP is thought to lead to an increased glomerular filtration rate and urine flow rate (51) and therefore is antagonistic to the renin-angiotensin-aldosterone and vasopressin systems. As exercise intensity increases, the release of the water and sodium conserving hormones increase sufficiently to offset the effects of ANP, thereby reducing the glomerular filtration rate and urine flow rate (51). However, according to Freund et al. (50) the elevated ANP levels during strenuous exercise may be important in the control of blood pressure responses to exercise and the shift of fluid from the vascular to extravascular spaces. It is also possible that the rise in ANP seen during exercise buffers the effect of vasopressin (50).

Freund et al. (51) postulated that the relative intensity of exercise is of greater importance for increases in ANP than the absolute work rate, which is similar to the other fluid-regulating hormones (aldosterone, vasopressin, and renin). There is little evidence about the effects of exercise duration on ANP levels. However, it would seem that with prolonged exercise there is a reduction in the stimulus for ANP production owing to the decreased PV and cardiac filling pressures (51).

e) Effect of Training

The role of volume-regulating hormones in the induction of hypervolemia remains to be determined. It holds that if expanded vascular volumes are to be maintained, mechanisms must exist to sustain these elevated volumes. It is generally believed that endurance training does not result in significant alterations of resting concentrations of renin, aldosterone, or vasopressin (147). Similarly, exercise training generally does not result in an attenuation of the response to exercise at similar relative work rates (49, 149). Atrial natriuretic peptide at rest also seems to be similar between endurance trained subjects and untrained controls and there is no difference between the groups with regards to the ANP response to maximal exercise (51). Whereas, the plasma concentrations of these hormones are generally reduced at a given absolute work rate (22, 149).

However, despite the general belief that training does not alter resting plasma concentrations of the volume-regulation hormones, considerable debate remains, especially with regards to plasma renin activity. Several longitudinal investigations have observed a fall in resting plasma renin activity after training (53, 72) and other cross-sectional investigations have shown lower plasma renin activity in athletes than in their untrained counterparts (134). Hespel et al. (72) postulated that physical training suppresses the renin-angiotensin-aldosterone. Given these discrepancies, it is important to gain further information of the hormonal adaptations to prolonged exercise.

f) What Role Do the Volume-regulating Hormones Play in the Induction of Hypervolemia?

The role of the volume-regulating hormones in the induction of hypervolemia is unclear. Convertino (16) postulated that two mechanisms may allow an expanded BV to be maintained: 1) total vascular capacitance may be increased, and 2) the gain in the volume-regulating reflex mechanism may be reduced. An attenuated sensitivity of the volume-regulating reflex mechanisms has received more experimental support than an increased capacitance (16, 23, 55, 98, 99).

A modification of the volume-regulating hormonal response to exercise and an expanded BV may occur as a result of endurance training. Convertino et al. (19)

examined the time course of BV expansion during a 8 day (2 hr/day at 65% $\dot{V}O_2$max) training protocol. Blood volume increased 8%, as a result of an increase in PV (12%) and a maintenance of RCV. Concurrently, plasma albumin content increased (~15%). Despite the increased PV and plasma albumin content, plasma osmalility remained unchanged. The authors postulated that the isotonic increase in total solute content (e.g., electrolytes and proteins) indicated that the volume-regulatory hormones stimulation with exercise resulted in an enhanced retention of fluids aiding in the expansion of BV. They concluded that two mechanisms are clearly associated with the exercise-induced BV expansion: 1) increased plasma protein content (specifically albumin), and 2) an increased retention of water and sodium, perhaps as a result of the continual stimulation of the renin-angiotensin-aldosterone systems.

Luetkemeier et al. (91) recently examined the effect of an aldosterone inhibitor, spironolactone, to see what role aldosterone plays in the induction of PV expansion after 3 days of endurance cycling. They found that the inhibition of aldosterone resulted in an attenuation of the increase in PV after exercise. They concluded that approximately "two-fifths of the plasma volume expansion induced by 3 d of endurance cycling could be attributed to aldosterone activity, and the remaining three-fifths could be explained by the expansion of intravascular protein mass." However, according to Wade (149) there was no evidence of alterations in plasma sodium levels, which suggests that aldosterone levels were still adequate and may not have played as large a role as Luetkemeier and coworkers postulated.

A chronic increase in plasma albumin content is commonly found coincident with the increased PV after endurance training (16, 19, 20, 66, 149). However, as previously discussed many investigations have reported normal levels of the volume-regulating hormones after endurance training. This is contradictory and may represent a resetting of the pressure mechanisms controlling the volume-regulating hormones.

In particular, it has been postulated that the sensitivity of the low-pressure cardio-pulmonary baroreceptors may be modified in response to exercise training (16, 23, 27, 98, 140). An alteration in these low pressure baroreceptors may result in a modification of the volume-regulating hormones' response to an expanded BV. This concept is supported by a reduced or attenuated diuresis and hormone (vasopressin) response during water immersion in athletes (9, 15, 134).

Several investigations (23, 24, 54, 55, 94-99, 108, 140) have revealed that the sensitivity of the cardio-pulmonary baroreceptors reflex is attenuated as a result of endurance training and this reduced sensitivity is associated with higher levels of BV. However, it is unclear whether the reduced sensitivity of the cardio-pulmonary baroreceptors is "the consequence rather than the cause of an increase in blood volume during exercise training" (98).

11.0 The Upper Limits to Physical Performance

As discussed previously, endurance training results in enhancements in cardiovascular function, which are generally of benefit for sport performance and/or daily living. However, recent research has examined the relationship between prolonged, strenuous exercise and several adverse outcomes. For instance, several investigators have revealed that prolonged strenuous exercise may take trained and untrained individuals to or beyond the limits of their cardiovascular system.

Findings after extreme exercise include the breakdown of red blood cells (36, 111, 156), lowered plasma concentrations of sodium (109), potassium (89) and/or magnesium (48, 90, 123, 127, 141), left ventricular dysfunction (35, 71, 107, 131) and/or delayed electrical activation of the myocardium (6, 155). These outcomes have been associated with a limitation to physical performance and potentially fatal complications including pulmonary edema, convulsions, respiratory arrest, cardiac arrhythmias, and sudden death (101, 102). Therefore, the understanding of the adaptations to exercise and the limitations to performance are important for the minimization of the risks associated with extreme exercise.

Conclusions

Endurance training results in a series of central and peripheral adaptations that are of benefit for sport performance and optimal living. Recent research has indicated that endurance athletes may have an increased capacity to utilize the Frank-Starling during incremental to maximal exercise. Blood volume has been shown to play a key role in the enhanced cardiovascular function of athletes. In fact, (27, 85, 154) endurance-trained athletes may be at an optimum BV for aerobic performance as result of their extensive training.

Given the impact of BV on cardiovascular performance, programs which optimize BV gains should be evaluated. Currently, little is known about what form of training regime leads to the greatest improvements in BV, aerobic performance, and myocardial morphology and function. Therefore, further evaluation of the effects of different forms of aerobic training on BV and cardiovascular function is warranted.

Finally, although exercise training leads to several adaptations that are of benefit to both performance- and health-related fitness, extreme exercise, such as the ultraendurance triathlon may take trained individuals to the limits of their cardiovascular system. Several adverse outcomes have been associated with prolonged strenuous exercise. Therefore, the further understanding of changes in cardiovascular function resulting from prolonged exercise would be useful to exercise physiologists and cardiologists alike.

Table 2.1: Average blood volume, maximum aerobic power and maximal stroke volume values reported in cross-sectional investigations.

Investigation (Ref)	n	A (yr)	G	TS	BV (mL)	BV (mL·kg^{-1})	ΔBV (%)	Tech	VO_2max (mL·kg^{-1}·min^{-1})	ΔVO_2max (%)	SVmax (mL)	ΔSVmax (%)
Brotherhood	12	27	M	UT	4616	75	25	CO	50.4	46	-	-
(10)	40	27	M	T	5752	93			73			
Carroll	9	67	M & F∫	UT	4248	63	10	E	23.7	9	-	-
(12)	29	68	M & F∫	T	4644	69			25.9			
Coyle (28)	9	25	M	UT	5534	70	-	E	48.5	-	-	-
Dill	48	20	M	UT	5657*	85	21	CO	-	-	-	-
(34)	12	20	M	T	6593*	104			73.2			
Gledhill	7	22	M	UT	4457	64‡	20	E	44.1	55	129	41
(61)	7	23	M	T	4994	77‡			68.6		183	
Hagberg	12	58	M	UT	4910	64&80‡	19&13‡	^{125}I	34.2	50	110*	27
(68)	7	56	M	T	5360	76&90‡		^{51}CR	51.3		140*	
Hopper	7	24	M	UT	5472	72&84‡	17&10‡	E	44.5	40	-	-
(75)	10	24	M	T	5640	83&92‡			62.1			
Kanstrup (80)	5	25	M	MT	5380	75*	-	^{51}CR	63.8	-	-	-

Table 2.1 Continued

Investigation (Ref)	n	A (yr)	G	TS	BV (mL)	BV (mL·kg^{-1})	ΔBV (%)	Tech	VO$_2$max (mL·kg^{-1}·min^{-1})	ΔVO$_2$max (%)	SVmax (mL)	ΔSVmax (%)
Kjellberg	92	38	F	UT	4070	62*	44	CO	-	-	-	-
(84)	8	26	F	T	5670	89*						
	174	24	M	UT	5250	75*	20	CO	-	-	-	-
	14	36	M	T	6580	90*						
	23	27	M	T	7450	103*	-	CO	-	-	-	-
Krip (85)	6	22	M	UT	5604	85‡	14	E	41.5	55	130	32
	6	25	M	T	6499	97‡			64.1		171	
Parker Jones	12	29	F	UT	4563*	73	21	E	35	53	-	-
(112)	15	31	F	T	4946*	88			53.7			
	12	60	F	UT	4368*	61	34	E	22.9	73	--	-
	13	58	F	T	4904*	82			39.7			
Pivarnik	9	29	F†	UT	5053	71	25	E	--	-	-	-
(116)	5	29	F†	T	6166	88						
Sawka	51	22	M	UT	5180*	69&82‡	-	^{125}I	53.5	-	-	-
(130)								^{51}CR				

Table 2.1 Continued

Investigation (Ref)	n	A (yr)	G	TS	BV (mL)	BV (mL·kg^{-1})	ΔBV (%)	Tech	VO$_2$max (mL·kg^{-1}·min^{-1})	ΔVO$_2$max (%)	SVmax (mL)	ΔSVmax (%)
Stevenson (142)	17	56	F	UT	4336	64&96‡	39	E	26.5	45	-	-
	13	55	F	T	4964	89&106‡	10‡		48.6			
Warburton (154)	9	22	M	T	6648	104‡	-	E	68.9	-	160	-
Yoshida (161)	12	20	M	UT	5150*	85&94‡	--	E	48.7	–	–	-

n, number of participants; *A*, age; *G*, gender; *TS*, training status; *T*, trained athletes; *UT*, untrained participants; *MT*, moderately trained participants; *BV*, blood volume; *ΔBV*, relative blood volume percent difference between UT and T; *Tech*, technique used to determine BV; *E*, Evan's blue dye; *CO*, carbon monoxide rebreathing; *^{51}CR*, radiochromate labelled erythrocytes; *^{125}I*, iodine-labelled albumin; *VO$_2$max*, maximal oxygen consumption; *ΔVO$_2$max*, percent difference in VO$_2$max between UT and T; *ΔSVmax*, percent difference in maximal stroke volume (SVmax) between UT and T; *, calculations based on reported values; †, values reported are those of pregnant women at 36 weeks of gestation; ‡, relative to lean body mass; ∫, data from both males and females were combined in the analyses; –, indicates data were not available.

Table 2.2: Average blood volume and maximal aerobic power values reported in longitudinal investigations.

Investigation (Ref)	n	A (yr)	G	Dur (days)	Int (%)	Time (min)	TS	BV (mL)	BV (mL·kg^{-1})	ΔBV (%)	Tech	VO_2max (mL·kg^{-1}·min^{-1})	ΔVO_2max (%)
Carroll	38	68	M & F∫	-	-	-	BT	4120	62	11	E	23.3	11
(12)				78	75-84	30-45	AT	4644	69			25.9	
Convertino	14	36	M	-	-	-	BT	5040	65	9	E	37.2	20
(23)				40	75-80	30	AT	5420	71			44.7	
Coyle (27)	8	25	M	~6 yrs	70-80	60	T	5177	76*	-9	E	64.5	-6
				14-28	0	0	DT	4692	68*			60.6	
Fortney	9	24	F	-	-	-	BT	4710*	78*	9	CO	37.9	-
(46)				28	40	90	AT	5120*	85*			-	
Glass	10	21	M	-	-	-	BT	5779*	83	-1	^{11}CO	-	-
(57)				60	-	-	AT	5861*	82				
Green	4	22	M	-	-	-	BT	5798	79*	5	^{131}I	52.8	-
(66)				3	120	~24	AT	6059	82*			-	
Green	8	21	M	-	-	-	BT	5247	72*	12	^{131}I	45.9*	1
(63)				4	71	120	AT	5876	80*			46.5*	
Green	7	21	M	-	-	-	BT	5247*	75*	11	^{131}I	48.5	-
(64)				3	65	120	AT	5877*	83*			-	

Table 2.2. Continued

Investigation (Ref)	n	A (yr)	G	Dur (days)	Int (%)	Time (min)	TS	BV (mL)	BV ($mL \cdot kg^{-1}$)	ΔBV (%)	Tech	VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	ΔVO_2max (%)
Green	7	21	M	-	-	-	BT	5315	70*	10	^{131}I	45.1	17
(65)				~40-48	62	120	AT	5879	77*		^{51}CR	52.6*	
Luetkemeier	10	29	M	-	-	-93	BT	5186	80*‡	9	E	56.7	-
(92)				3	68		AT	5676	88*‡			-	
Mier	8	25	F	--	--	--	BT	3981*	63	5	E	33.2*	12
(104)				10	80-95	60	AT	4166*	66			37.3*	
	8	29	M	--	--	--	BT	5198*	68	7	E	40.8*	9
				10	80-95	60	AT	5560*	72			44.5*	
Mier	10	26	M & F∫	-	-	-	BT	4659	66*	6	E	35.4	10
(105)				10	65-95	60	AT	4951	70*			38.9	
Pugh	6	21	M	-	-	-	BT	5145*	78	4	CO	--	--
(121)				1	-	480	AT	5349*	81*				
Ray	8	25	M	-	-	-	BT	4951	62*	2	^{99m}TC	-	23 & 16▾
(122)		24		32	50-100∮	40	AT	5013	63*				
	8	24	M	-	-	-	BT	4722	60*	8	^{99m}TC	-	6 & 15▾
				32	50-100†	40	AT	5104	65*				

Table 2.2. Continued.

Investigation (Ref)	n	A (yr)	G	Dur (days)	Int (%)	Time (min)	TS	BV (mL)	BV $(mL \cdot kg^{-1})$	ΔBV (%)	Tech	VO_2max $(mL \cdot kg^{-1} \cdot min^{-1})$	ΔVO_2max (%)
Richardson	14	34	M	–	–	–	T	5615	80•	4	E	60.7	1
(125)				2	90-95	40-55	AT∲	5804	83•			61.1•	
Shoemaker	7	21	M	–	–	–	BT	5233	7374	2	^{125}I	48.1	15
(133)				44-55	68	120	AT	5322				55.3	
Stachenfield	9	71	F	–	–	–	BT	3778	61•	-2	E	24.8	10
(140)				72-96	60-75	30-50	AT	3775	60•			27.7	

n, number of participants; *A*, age; *G*, gender male (M) or female (F); *Dur*, duration of training or detraining; *Int*, intensity of training expressed as a percentage of maximum; *Time*, minutes of training per day; *TS*, training status; *BT*, before training; *AT*, after training; *DT*, after detraining; *ΔBV*, relative blood volume percent difference between untrained or detrained and trained; ‡, relative to lean body mass; *ΔVO_2max*, percent difference in VO_2max between UT or DT and T; *Tech*, technique used to determine blood volume; *E*, Evan's blue dye; *CO*, carbon monoxide; *^{11}CO*, radiolabelled carbon monoxide; *^{51}CR*, radiochromate labelled erythrocytes; *^{125}I & ^{131}I*, iodine-labelled albumin; *^{99}Tc*, Technetium 99m labelled erythrocytes; •, calculations based on reported values; ∫, data from both males and females were combined in the analyses. †, interval training in the upright position; ⨍, interval training in the supine position; ▾, percent change in VO_2max in the supine and upright positions, respectively; –, indicates data were not available; ∲, already trained (T) participants were further trained.

Table 2.3. Summary of investigations examining the effects of acute plasma volume expansion and/or reduction on exercise cardiovascular function.

Investigation (Ref)	n	Age	Gender	Training Status	BVctrl (mL)	BVpost (mL)	ΔBV (mL)	ΔBV (%)	VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	ΔVO_2max (%)	ΔSVmax (%)
Coyle (27)	8	25	M	T	5177	5605	429	8	64.5	No Change	-
				DT	4692	5412	720	15	60.6	3	-
Coyle (28)	9	25	M	UT	4876	5094	218	5	48.5	4	-
						5455	579	12	48.5	No Change	-
Hopper (75)	7	24	M	UT	4961	5354	393	7	44.5	--	-
	10	24			5640	5594	633	11	44.5	--	-
	10	24	M	T	5640	6000*	400	7	62.1	--	-
Kanstrup (79)	14	27	M	MT	5480	6170	700	13	59.6*	No Change	20
Kanstrup (80)	5	25	M	MT	5380	6280	790	16	63.8*	No Change	-
Kanstrup (82)	11	26	M&F	UT	5220	5710	490	9	--	--	-
Krip (85)	6	22	M	UT	5604	6150	546	10	41.5	7	9
	6	25	M	T	6499	6014	-486	-7	64.1	-13	-14

Table 2.3. Continued.

Investigation (Ref)	n	Age	Gender	Training Status	BVctrl (mL)	BVpost (mL)	ΔBV (mL)	ΔBV (%)	VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	ΔVO_2max (%)	ΔSVmax (%)
Luetkemeier (92)	10	29	M	T	5186	5638	400	9	56.7	–	-
Mier (104)	8	25	F	UT	4166*	-	292-375*	7 to 9	38	No Change	-
	8	29	M	UT	5198*	–	364-468*	7 to 9	47.9	No Change	-
Warburton (154)	9	22	M	T	6648	7195	547	8	68.9	No Change	3

n, number of participants; *T*, trained; *DT*, detrained; *MT*, moderately trained; *UT*, untrained; *BVctrl*, resting blood volume; *BVpost*, blood volume post plasma volume manipulation; ΔBV, change in BV; VO_2max, maximal oxygen consumption; ΔVO_2max, change in VO_2max; $\Delta SVmax$, maximal stroke volume; -, data not reported. Adapted from Warburton, et al. (154).

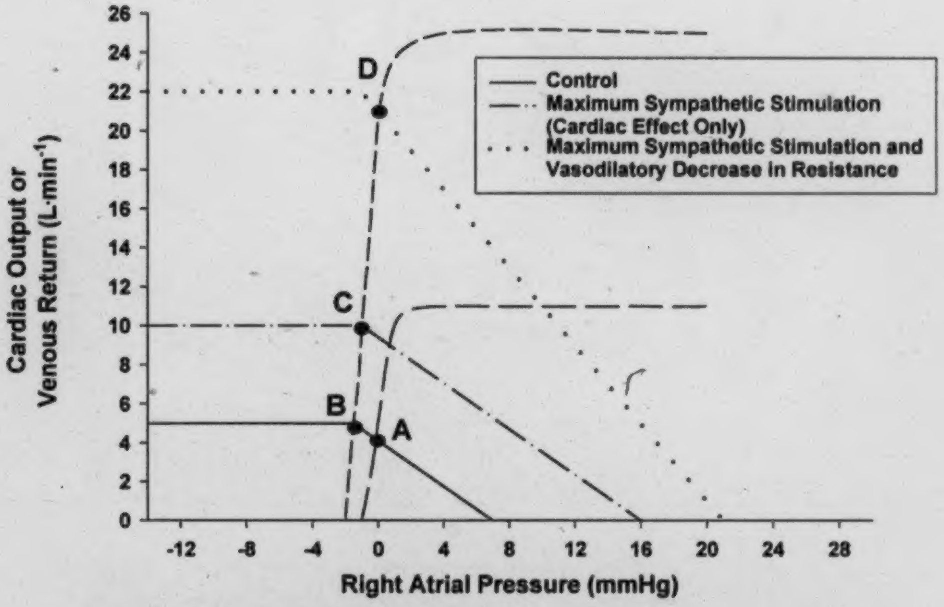

Figure 2.1. Cardiac function and venous return curves at varying sympathetic and vasodilatory levels. Adapted from Smith et al. Progress in Cardiovascular Disease 18(6):421-443, 1976 (Ref. 135).

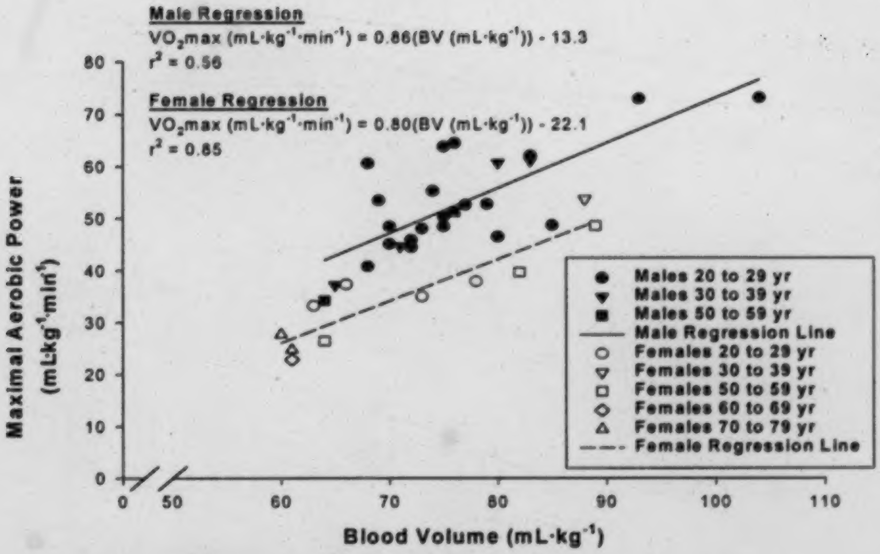

Figure 2.2. Relationship between maximal aerobic power and blood volume as a function of gender. Values are taken from reported means from both cross-sectional and longitudinal investigations (Tables 2.1 and 2.2).

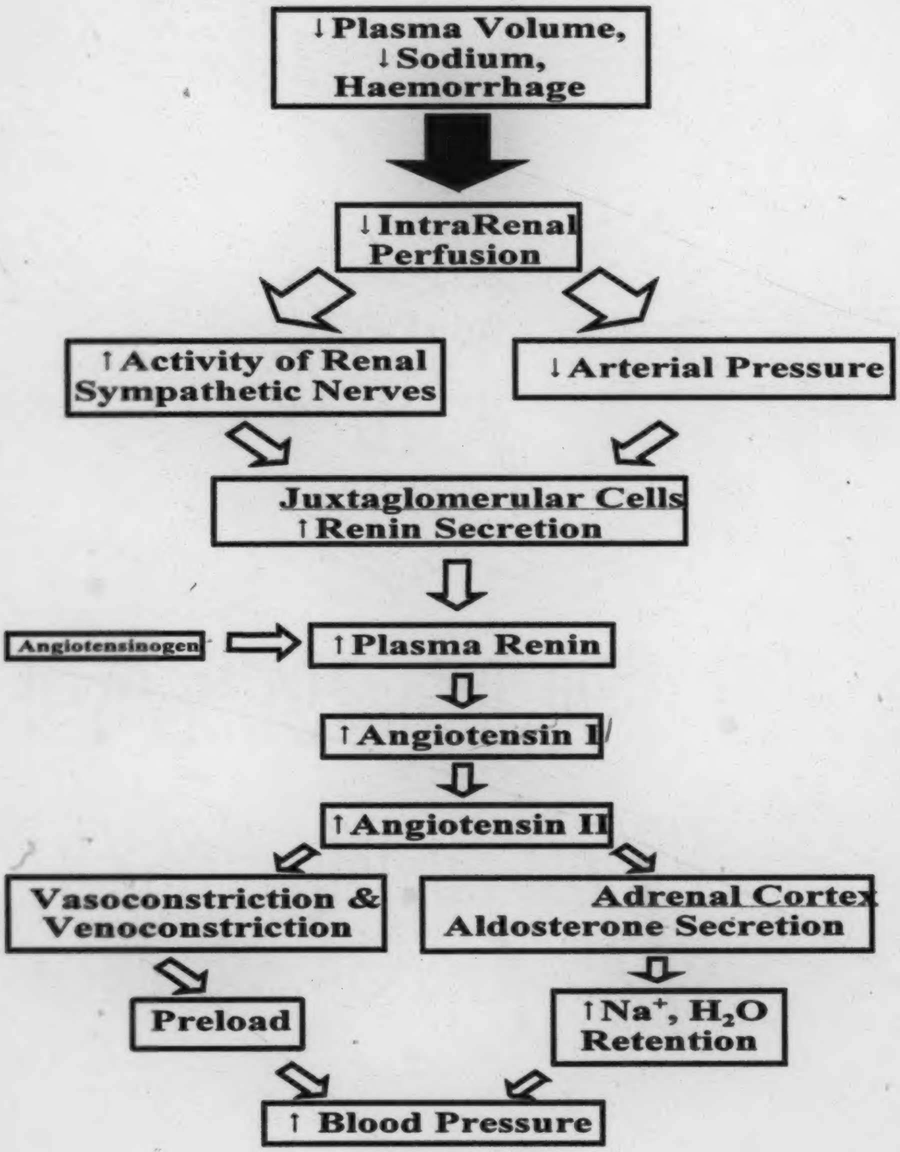
↓Plasma Volume,
↓Sodium,
Haemorrhage
↓IntraRenal Perfusion
↑Activity of Renal Sympathetic Nerves
↓Arterial Pressure
Juxtaglomerular Cells
↑Renin Secretion
Angiotensinogen
↑Plasma Renin
↑Angiotensin I
↑Angiotensin II
Vasoconstriction & Venoconstriction
Adrenal Cortex
Aldosterone Secretion
Preload
↑Na⁺, H₂O Retention
↑ Blood Pressure

Figure 2.3. The regulation of renal perfusion and plasma volume.

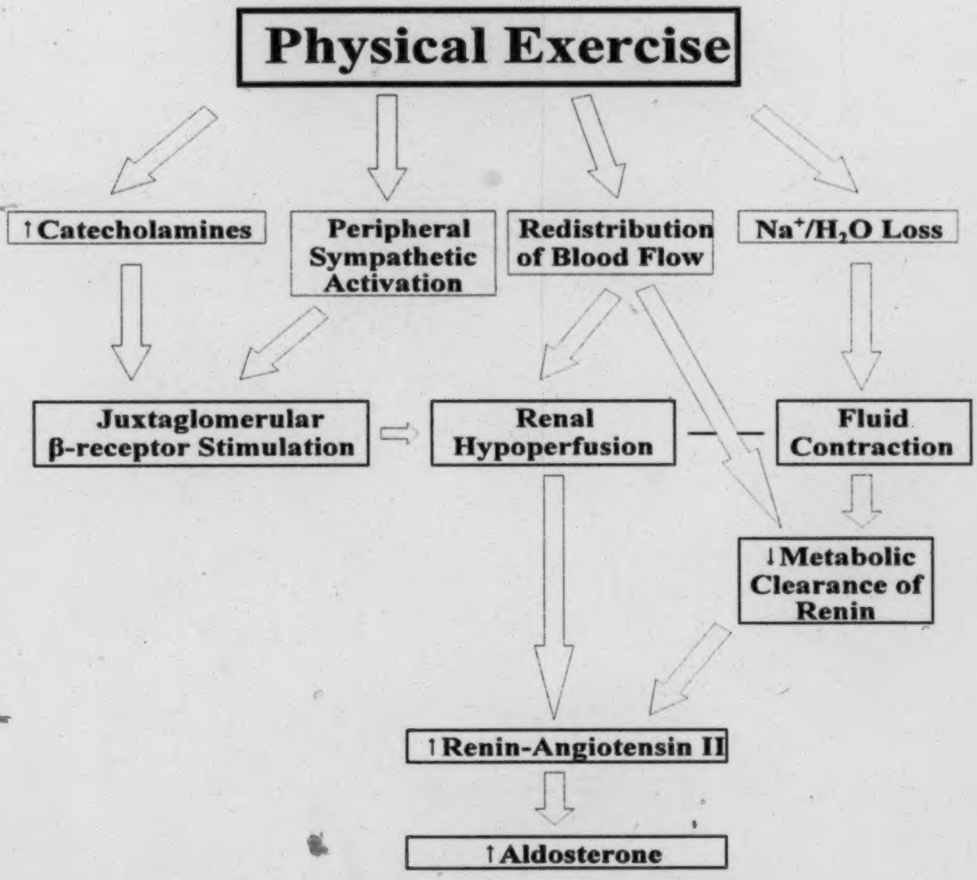
Physical Exercise
↑Catecholamines
Peripheral Sympathetic Activation
Redistribution of Blood Flow
Na⁺/H₂O Loss
Juxtaglomerular β-receptor Stimulation
Renal Hypoperfusion
Fluid Contraction
↓Metabolic Clearance of Renin
↑Renin-Angiotensin II
↑Aldosterone

Figure 2.4. Effect of physical exercise on the renin-angiotensin-aldosterone systems adapted from Fallo (43).

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CHAPTER THREE

Does the Stroke Volume of Endurance-trained Athletes Plateau at a Submaximal Work Rate during Exercise in the Supine and Upright Positions?

Abstract

Background: *Recent evidence indicates that the stroke volume of highly trained endurance athletes continues to increase throughout incremental to maximum exercise. This is contrary to the widely held belief that stroke volume reaches a plateau at a submaximal heart rate (irrespective of fitness level), owing to a limitation in the time for diastolic filling.* ***Purpose:*** *The primary purpose of this investigation was to evaluate cardiac responses to incremental exercise using a measurement technique, which allowed for the complete assessment of cardiac volumes during exercise conditions. A secondary purpose was to evaluate the effects of changes in postural position on the cardiovascular responses to incremental exercise. Thirdly, we sought to examine the myocardial oxygen demand brought about by incremental exercise in the supine and upright positions in highly trained endurance athletes.* ***Methods:*** *Ten highly trained male cyclists participated in this investigation* ($\dot{V}O_2max = 67.8 \pm 3.9$ $mL \cdot kg^{-1} \cdot min^{-1}$, $Age \pm SD = 26 \pm 5$). ***Results:*** *The athletes were able to increase their stroke volume during incremental to maximal exercise in both the upright and supine positions, in the face of a reduced time for diastolic filling. These data suggest that the athletes made use of the Frank-Starling mechanism to increase their stroke volume throughout exercise. The percent changes in end-diastolic volume and stroke volume were greater in the upright position versus the supine position. The increases in cardiac output during exercise in both the upright position were related to changes in heart rate, myocardial contractility and the use of the Frank-Starling mechanism. The athletes experienced a 4- to a 5-fold increase in myocardial oxygen consumption during incremental exercise.* ***Conclusions:*** *Highly trained endurance athletes make use of the Frank-Starling mechanism throughout incremental to maximal exercise. Postural position has a significant effect on the relative contribution of heart rate, myocardial contractility, and the Frank-Starling mechanism to the increase in cardiac output during exercise conditions. Myocardial oxygen consumption during incremental exercise is similar to that observed in untrained individuals.*

BACKGROUND

Cardiac output ($\dot{Q}$) increases throughout incremental exercise as the result of increases in heart rate and stroke volume (SV). The common explanation for the observed increases in $\dot{Q}$ during the later stages of vigorous exercise in normally active and trained participants was that tachycardia (an accelerated heart rate) and myocardial contractility (an increased contraction vigor) were primarily responsible. However, this notion has recently been challenged (19, 31, 59).

At low and moderate exercise intensities, the Frank-Starling mechanism is thought to be mainly responsible for the observed increases in SV and thus $\dot{Q}$ in endurance-trained and normally active individuals (18, 21, 42). This occurs due to increased filling during diastole (i.e., an increased end-diastolic volume (EDV)), and therefore an increased SV (due to the Frank-Starling effect).

Stroke volume is thought to reach a plateau at a submaximal work rate of approximately 40% maximal oxygen uptake ($\dot{V}O_2$max) (2). Researchers believe that this plateau occurs because tachycardia limits the time available for diastolic filling, thereby limiting the volume of blood entering the heart during diastole (i.e., EDV) in both trained and untrained individuals (18, 25, 42). It is therefore hypothesized that increased myocardial contractility and tachycardia have more effect on increasing $\dot{Q}$ than the Frank-Starling mechanism during the later stages of vigorous exercise (18, 28, 42). An increased myocardial contractility is thought to result in an increased ejection of blood (i.e., a greater ejection fraction (EF)) leading to a decreased volume of blood remaining in the ventricle at the end of systole (i.e., end-systolic volume (ESV)), which allows SV to be maintained despite a reduction in EDV.

Recent investigations and previously overlooked findings (13, 19, 31, 44, 46, 50, 59, 60, 62) indicate that endurance athletes may rely on different mechanisms to increase their $\dot{Q}$ during the later stages of vigorous exercise. For instance, recent investigations using highly trained endurance athletes and techniques which allow for the determination of SV and/or EDV during maximal exercise have shown that endurance-trained athletes may have an increased ability to utilise the Frank-Starling mechanism during maximal exercise. This increased ability is thought to be primarily due to an enhancement in ventricular filling, which may be related to an increased preload in endurance athletes (19, 31). Therefore, authors have postulated that endurance-trained athletes may make more use of the energy-efficient Frank Starling mechanism during strenuous exercise than their untrained counterparts (19, 31, 59).

Myocardial oxygen consumption ($M\dot{V}O_2$) during incremental exercise in the supine position in healthy individuals has also gained recent interest (30). Investigators commonly estimate $M\dot{V}O_2$ by using the product of heart rate and blood pressure (i.e., the rate-pressure-product (RPP))(39). Research with the canine model has also shown that the pressure-volume area (PVA) (during a single cardiac cycle) is proportional to $M\dot{V}O_2$ (30, 51-53). Kanstrup and coworkers (30) have recently demonstrated that radionuclide ventriculography can be used to evaluate $M\dot{V}O_2$ in healthy humans. However, very little is known about the radionuclide assessment of $M\dot{V}O_2$ in highly trained endurance athletes during exercise in the supine and/or upright positions.

Therefore, the primary purpose of this investigation was to determine whether endurance-trained athletes make use of the Frank-Starling mechanism during the later stages of vigorous exercise. Secondly, we sought to determine whether changes in postural position elicit changes in the cardiovascular response to exercise. Thirdly, we were interested in examining the effects of postural changes on $M\dot{V}O_2$.

RESEARCH PROCEDURE

Ten highly trained male cyclists between the ages of 18 and 30 participated in this investigation with informed consent and medical clearance. All research was approved by the University of Alberta's Ethics Committee for Human Research. All participants possessed a $\dot{V}O_2$max of 60 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ or greater. Baseline clinical characteristics are illustrated in Table 3.1. Participants were required to undergo four incremental exercise protocols to maximum on a cycle ergometer: two exercise protocols during a familiarization session and two exercise protocols during the test day (in the supine and upright positions, respectively). All testing was conducted at the Exercise Stress Laboratory at the University of Alberta Hospital. Throughout the investigation, all participants were in the maintenance phase of their training regimen (i.e., reduced volume during their in-season training).

Familiarization Session

Prior to the test day, participants underwent one familiarization session during which they were oriented to incremental cycle ergometer exercise and all aspects of the testing protocol. During the familiarization session, all participants had their $\dot{V}O_2$max determined on a cycle ergometer during upright cycle ergometer exercise employing incremental mutli-stage work rates to maximum. To ensure that the participants achieved $\dot{V}O_2$max, following the incremental exercise test, they rested for one minute then performed a supramaximal work rate with a requirement of ~5% beyond their volitional peak work rate. Thirty minutes following the upright exercise, participants were oriented to incremental to maximal exercise in the supine position. Measurements of aerobic and ventilatory performance were determined throughout (as described later) using standard laboratory techniques. Also, the work rates which elicited the predetermined heart rates of 110, 130, 150 beats·min^{-1} and maximal heart rate were determined at this time in each postural position. Staged heart rates were used to control for the differences in diastolic and systolic function owing to heart rate (19, 31, 59).

Experimental Test Day

During the test day, participants cycled at the predetermined work rates of 110, 130, 150 beats·min^{-1} and maximal heart rate during supine and upright exercise. The order of the supine or upright exercise was randomly counterbalanced between participants to eliminate the possibility of an order effect from confounding the results of the investigation. Group A underwent supine exercise first followed by upright exercise, in comparison to Group B who underwent upright exercise first followed by supine exercise. Blood samples were taken prior to exercise and 30 min after the completion of the first exercise bout to control for differences in hydration between exercise conditions. Participants were not permitted to commence the second exercise bout until their resting haematocrit levels had returned to baseline conditions. This precaution was taken to ensure to control for differences in vascular volumes between testing conditions. Cardiac function was determined using radionuclide ventriculography at each staged heart rate (as described later). Oxygen consumption was monitored continuously via a calibrated metabolic system throughout exercise (as described later).

MEASUREMENT TECHNIQUES

Incremental Exercise Tests

The exercise test protocol consisted of incremental to maximum exercise on an electronically braked cycle ergometer (59). The resistance on the ergometer was progressively increased to elicit staged steady-state conditions at predetermined target heart rates (± 5 beats) of 110, 130, 150 beats$\cdot$min^{-1} to maximum. Participants were allowed to self-select their pedalling cadence, but the participants generally chose a cadence of 80 to 90 revs$\cdot$min^{-1}. Each exercise stage was approximately four min in duration and no rest was provided between stages. Measures of $\dot{V}O_2$ and heart rate were taken continuously throughout each stage of exercise. Radionuclide measures of LV function were taken two min into each stage (after a steady state had been achieved) followed by the measurement of blood pressure.

Oxygen Uptake

Oxygen uptake was measured using open circuit spirometry (54). Expired gas and ventilatory parameters were assessed using a calibrated metabolic system (Quinton Metabolic Cart, California). The metabolic system was calibrated for volume and concentrations of oxygen and carbon dioxide before and after each exercise test. The major criteria for the establishment of $\dot{V}O_2$max was the fulfillment of a plateau in $\dot{V}O_2$. Secondary criteria included: 1) volitional fatigue, 2) attainment of predicted maximal heart rate, or 3) a respiratory exchange ratio greater than 1.10.

Haematocrit

Venous blood was drawn from a cathelon placed in an antecubital vein immediately before each exercise bout on the test day according to the technique of Forster et al. (16). Haematocrit was determined in quadruplicate using the microcentrifuge method according to standard laboratory procedures.

Determination of Heart Rate and Blood Pressure During Incremental Exercise

During all testing sessions, heart rate was continuously monitored with a 12 lead electrocardiogram (ECG). Blood pressure was determined with a sphygmomanometer and a stethoscope placed on the participant's right arm, while seated on the cycle ergometer (duplicate measures using this procedure during exercise conditions are generally within ± 5%). Measurements were made during rest and at every predetermined stage of exercise during the incremental exercise tests (approximately every 4 min) and immediately upon the cessation of exercise.

Radionuclide Ventriculography During Incremental Exercise

Radionuclide ventriculography was conducted at rest and during incremental exercise on all test days. Approximately 1.0 to 3.0 mL of autologous whole blood was labelled in vivo with 1 Gigabequeral Technetium Pertechnetate (Gbq Tc-99m) following in vivo sensitization of the red blood cells with 1.0 mg Stannous Phyrophosphate. Two 5 mL blood samples were drawn at the end of the scan to determine blood count density via the already established intravenous line.

Radioactive imaging was performed at least 5 minutes after labelled red blood cell infusion in synchrony with the R-wave of the ECG. The gating circuit was such that the scintillation camera was only turned on during selected portions of the cardiac cycle (i.e., end-diastole and end-systole). Gated blood pools scans were acquired in a ~40° left anterior oblique projection (to best separate the right and left ventricles) with the participant in the supine or upright position. Images were acquired using a low energy, parallel-hole collimeter attached to a small field of view (200 mm diameter crystal) gamma camera. Equilibrium acquisitions were taken at rest and at each of the exercise stages. Each measurement period was approximately 4 minutes in duration, with the radionuclide acquisition being taken during the last two minutes of each stage. Quantification of left ventricular EF, EDV, ESV, time to peak filling (TPF), time to peak ejection (TPE), peak filling rate (PFR), and peak ejection rate (PER) were calculated using commercial software by a radionuclide technician who was blind to the treatment condition of the participant. Left ventricular EF was determined from background corrected counts within the end-diastolic and end-systolic regions of interest. Left ventricular SV was determined as EDV minus ESV, and $\dot{Q}$ was determined as SV times HR. According to the review of Warburton et al. (58) the test retest reliability of radionuclide ventriculography is similar to other measures of cardiac function (i.e., ± 10%).

Radionuclide Assessment of Blood Volume

To assess baseline blood volume, ~5 mL of blood 10 min was withdrawn after the radionuclide tracer administration (during the testing session before exercise) from an antecubital vein. Determination of the level of radioactivity in the 5 mL sample and assessment of the total radioactive dose administered (correcting for the amount initially in the syringe and the amount remaining after administration) allowed for the measurement of total BV using the dilution principle (6, 44). The calculation used in the determination of BV using this method was as follows:

$$\text{Blood Volume (mL)} = \text{Blood Sample (mL)} \cdot [(\text{DF} \cdot \text{Activity Administered} - \text{Residual Activity})] / (0.91 \cdot \text{Sample Activity}),$$

where blood sample is the volume of blood withdrawn (~5 mL) post-infusion of the Tc-99m; DF, is the decay factor for the Tc-99m according to time; Activity Administered, is the dose of Tc-99m administered; Residual Activity, is the remaining activity in the syringe after the activity was administered; 0.91 is the correction for venous to whole body blood ratio; Sample Activity, is the activity in the post-infusion blood sample.

Myocardial Oxygen Consumption

Myocardial oxygen consumption was estimated using the product of heart rate and blood pressure (i.e., RPP ($\text{mmHg} \cdot \text{min}^{-1}$)) and calculated according to original methods of Suga and coworkers (53) as described by Kanstrup et al. (30). Briefly, $M\dot{V}O_2$ was considered to be proportional to the PVA as calculated by the total of stroke work (SW) and potential energy (PE) during systole (Figure 3.1) (30). Stroke work was calculated using the formula (DBP + (SBP - DBP)/2) · SV, where DBP is diastolic blood pressure and SBP is systolic blood pressure. The PE was calculated as ESV·SBP/2, with the assumption that the ventricular volume at zero pressure was equivalent to zero (30). The estimated $M\dot{V}O_2$ was calculated according to the formula of Suga and coworkers

(53). $\dot{M}VO_2$ (mL $O_2 \cdot 100\ g^{-1} \cdot min^{-1}) = (1.75 \cdot 10^{-5} \cdot PVA + 0.03) \cdot HR$, where HR equals heart rate. The net myocardial efficiency was calculated according to the formula: Net myocardial Efficiency = (0.38·SW)/PVA (30, 52). All estimations of $M\dot{V}O_2$ were made with the assumption that the errors resulting from the indirect measures of intra ventricular pressures are negligible (30).

STATISTICS

Descriptive and inferential statistical analyses of all data were conducted using STATISTICA™. The acceptable level of significance was set *a priori* at $p \leq 0.05$. All measurements subjected to inferential analyses were reported as mean and standard deviation of the mean (SD). The cardiorespiratory measurements were analyzed using a three-way repeated analysis of variance (ANOVA) (two levels of condition, two levels according to order, and five levels of heart rate). Tukey *post hoc* comparisons were used to identify differences between means when main effects were observed. Simple linear regression and forward stepwise linear regression were utilized to establish the relationship(s) between the cardiovascular parameters of interest.

RESULTS

The mean results for total blood volume, plasma volume, red blood cell volume and $\dot{V}O_2$max at baseline are shown in Table 3.1. The three-way ANOVA revealed that treatment order had no significant impact on the dependent variables of interest, thus an order effect was unlikely. Because there was no order effect differences between groups A and B, these groups were merged and all data reported are expressed as the mean ± SD from all ten participants during supine or upright exercise.

Oxygen Consumption

Oxygen consumption (in both absolute and relative terms) increased in a linear fashion throughout incremental exercise in both the supine and upright positions (Figures 3.2 and 3.3). No significant difference existed between the supine and upright conditions during incremental exercise. However, the participants were able to attain a higher $\dot{V}O_2$max (10.3%) during upright exercise in comparison to supine exercise (63.0 ± 5.5 vs 57.2 ± 5.4 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively). The athletes commonly complained of an enhanced muscular fatigue and inability to use their body weight to meet the demands of the later stages of exercise.

Cardiac Output

The changes in $\dot{Q}$ throughout incremental exercise in the supine and upright positions are illustrated in Figure 3.4. Supine exercise resulted in a slightly larger $\dot{Q}$ than upright exercise at rest and throughout incremental exercise ($p = 0.052$). Cardiac output increased throughout incremental exercise in both exercise positions (Figure 3.4).

To evaluate the relative changes in cardiovascular parameters associated with $\dot{Q}$ percent changes relative to rest were calculated. This permitted the assessment of the magnitude of changes in the parameters of interest irrespective of differences in vascular volumes owing to the effects of gravity. Percent changes in $\dot{Q}$ followed a similar pattern to the absolute changes in $\dot{Q}$ as illustrated in Figure 3.5. There were no significant differences with regards to percent changes in $\dot{Q}$ between supine and upright exercise.

Stroke Volume

Stroke volume increased throughout incremental exercise in both the supine and upright positions (Figure 3.6). The highest level for SV was reached during maximal exercise in both the supine and upright positions. However, statistical significance was only achieved up to a heart rate of 110 beats·min^{-1}. In absolute terms, SV was significantly larger throughout supine exercise in comparison to upright exercise (Figure 3.6). However, the percent change in SV during exercise was significantly greater in the upright position in comparison to the supine position (Figure 3.7).

End-diastolic Volume

End-diastolic volume followed a similar pattern to SV throughout incremental exercise in both the supine and upright positions (Figure 3.8). Supine exercise resulted in a significant increase in EDV in comparison to upright exercise at each staged heart rate (Figure 3.8). Percent changes in EDV also followed a similar pattern (Figure 3.9) to percent changes in SV. Upright exercise resulted in a significantly larger percent increase in EDV than supine exercise.

End-systolic Volume

End-systolic volume did not significantly change as a result of supine or upright exercise (although there is a clear trend for a reduction in ESV with increasing exercise intensities above 110 beats·min^{-1}) (Figure 3.10). There was also no significant difference between absolute ESV or percent changes in ESV (Figure 3.11) during supine and upright exercise. Percent changes in ESV also did not significantly change during incremental exercise.

Ejection Fraction

Ejection fraction followed a similar pattern during incremental exercise in both the supine and upright positions (Figure 3.12). Ejection fraction was significantly higher in the supine position versus the upright position (Figure 3.12).

Myocardial Contractility

The ratio of systolic blood pressure (SBP) to ESV (SBP/ESV) throughout incremental exercise is illustrated in Figure 3.13. There was no significant difference between SBP/ESV during supine or upright exercise. Percent changes in SBP/ESV followed a similar pattern to the absolute changes in SBP/ESV (Figure 3.14). No significant difference existed between supine and upright exercise with regards to SBP/ESV.

Time to Peak Ejection

No significant difference existed in time to peak ejection between the supine and upright positions (Figure 3.15). Time to peak ejection was significantly decreased in comparison to rest throughout exercise in both the supine and upright positions.

Time to Peak Filling

Time to peak filling was significantly longer in the upright position versus the supine position (Figure 3.16). Time to peak filling was significantly decreased in comparison to rest throughout exercise in both the supine and upright positions (Figure 3.16).

Peak Ejection Rate

Peak ejection rate as a function of incremental exercise in both the supine and upright positions is illustrated in Figure 3.17. There was no significant difference between supine and upright exercise.

Peak Filling Rate

Peak filling rate was significantly greater in the supine versus upright positions (Figure 3.18). Peak filling rate was significantly increased in comparison to rest throughout exercise in both the supine and upright positions.

Figures 3.19 a and 3.19 b compare the PFR and PER response to incremental exercise in the supine and upright positions, respectively. In both exercise positions, the PFR was consistently higher than the PER during incremental exercise (especially during the later stages).

Oxygen Pulse

Oxygen pulse, the ratio of $\dot{V}O_2$ to heart rate, is a product of SV and arterio-venous oxygen difference. The oxygen pulse response to supine and upright exercise is illustrated in Figure 3.20. Oxygen pulse increased in a linear fashion throughout incremental exercise in both the supine and upright positions (Figure 3.20).

Pressure-volume Relationships

Figures 3.21 and 3.22 illustrate the changes in the pressure-volume relationship during incremental exercise in the upright and supine positions. The intercept through the abscissa for the end-systolic pressure volume lines whose slope defines E_{MAX} (i.e., SBP/ESV ratio) (45) does not go through zero. This is the theoretical ventricular volume at zero pressure. These figures highlight the large changes in EDV and myocardial contractility throughout exercise in both the supine and upright positions.

The estimated PVA and its components during rest and exercise conditions in the supine and upright positions are illustrated in Figure 3.23. There were no significant differences between supine and upright exercise with regards to the calculated PVA. However, the supine position did have a slightly larger PVA than the upright position ($p = 0.057$). Stroke work accounted for the majority of the changes in PVA during exercise (Figure 3.23 B). The supine position resulted in a significantly greater SW in comparison to the upright position. There was a small increase in the PE during exercise in both positions. No significant difference existed in PE between the supine and upright positions.

The calculated $M\dot{V}O_2$ using the PVA parameters was not significantly different between the supine and upright positions (Figure 3.24). There was approximately a four-fold increase in calculated $M\dot{V}O_2$ from rest to maximal exercise in both the upright and supine positions. The net myocardial efficiency was not significantly different between postural positions (Figure 3.25).

Rate-pressure Product

Rate-pressure product increased in a linear fashion throughout incremental exercise in both the supine and upright positions (Figure 3.26). No significant difference existed between the supine and upright positions with regards to RPP.

The relationship between estimated $M\dot{V}O_2$ using the PVA calculations and estimated $M\dot{V}O_2$ using the RPP is illustrated in Figure 3.27. There was a linear relationship between RPP and estimated $M\dot{V}O_2$ from the PVA. The relationship between calculated $M\dot{V}O_2$ and RPP during supine exercise was: Calculated $M\dot{V}O_2$ ($mL\cdot 100g^{-1}\cdot min^{-1}$) = -3.975 + 0.002 (RPP ($mmHg\cdot min^{-1}$)), $r^2 = 0.74$, $p < 0.05$. The relationship between calculated $M\dot{V}O_2$ and RPP during upright exercise was: Calculated $M\dot{V}O_2$ ($mL\cdot 100g^{-1}\cdot min^{-1}$) = -5.329 + 0.002 (RPP ($mmHg\cdot min^{-1}$)), $r^2 = 0.75$, $p < 0.05$.

DISCUSSION

The primary purpose of this investigation was to evaluate the changes in SV and $\dot{Q}$ that occur during incremental to maximum exercise in the supine and upright positions. The endurance trained athletes involved in this investigation had high $\dot{V}O_2max$ (Mean = 67.8 $mL\cdot kg^{-1}\cdot min^{-1}$). Therefore, these athletes represent the high end of the aerobic power continuum. Previous research using techniques that allowed for maximal determinations of SV and $\dot{Q}$ in endurance trained athletes, with a similar $\dot{V}O_2max$, have shown that highly trained athletes may increase their SV throughout incremental exercise (19, 31, 59). These investigations postulated that endurance athletes may be able to make greater use of the Frank-Starling mechanism during the later stages of vigorous exercise than was previously thought. However, measures of ventricular volumes are impossible to evaluate with the measurement techniques that these authors used (57, 58). Therefore, the understanding of the mechanisms by which endurance athletes may increase their SV during incremental exercise remains to be fully discovered.

Radionuclide ventriculography provides a reliable non-invasive means to determine ventricular volumes during exercise conditions in healthy individuals and patients with cardiovascular disease (57, 58). Radionuclide ventriculography has been used with normally active and/or moderately trained individuals. However, to our knowledge no investigation has examined the volumetric changes in both the supine and upright positions in highly trained athletes. Therefore, this investigation provides us with an unique opportunity to evaluate the changes in SV during incremental exercise in the supine and upright positions of highly trained endurance athletes.

The cardiac volumes determined using radionuclide ventriculography tend to be lower than that achieved by other procedures, irrespective of the participant population (58). As such, comparisons of these absolute volumes with others investigators' findings would be inappropriate. However, this is a systematic error across the staged heart rates (58). Thus, the changes in these vascular volumes during incremental exercise in both the supine and upright positions can be safely compared to the findings of other investigators (57, 58).

Mechanisms Responsible for the Increase in Cardiac Output during Incremental Exercise

In the present investigation, $\dot{Q}$ increased throughout incremental to maximal exercise in both the supine and upright positions. Cardiac output has consistently been shown to increase during incremental exercise, generally reaching its peak value during maximal exercise (2, 19, 58, 59). The increases in $\dot{Q}$ are related to changes in its determinants (i.e., SV and heart rate).

Considerable controversy has arisen as the result of the finding that SV continues to increase throughout incremental exercise in highly trained endurance athletes. However, consideration of the components involved in the elevations of $\dot{Q}$ during exercise indicates that for $\dot{Q}$ to increase to the levels commonly observed in endurance trained athletes (i.e., 5- to 6-fold), SV must play a larger role than was once previously thought. According to Smith and coworkers (49) maximal $\dot{Q}$ is ultimately limited by venous return. As Smith et al. (49) wrote "sympathetic stimulation of the heart or of the peripheral circulation – or even both at the same – can have only moderate effects on cardiac output." Smith et al. (49) postulated that "if the change in heart rate and the increase in stroke volume are both maximal, then the cardiac output may increase 5-6 times the normal value" in exercising normal humans. Therefore, for $\dot{Q}$ to increase during vigorous exercise it is reasonable to argue that myocardial contractility, tachycardia and the Frank-Starling mechanisms are key factors.

Stroke Volume Response to Exercise

In the present investigation, SV increased throughout incremental exercise in the supine and upright positions. However, statistical significance was only achieved at a heart rate of 110 beats·min^{-1}. It may be argued that this is supportive of research which indicates that SV reaches a plateau at submaximal exercise intensities at around 110 to 130 beats·min^{-1} (1, 18, 25, 28, 30, 36, 42). However, these investigations commonly reported an initial increase in EDV followed by a sharp decline at maximal exercise (30). A consecutive decline in ESV has also been commonly observed during incremental exercise (1, 30). Others have reported a maintenance of EDV throughout incremental exercise (28), with a concomitant reduction in ESV. Both findings are suggestive of an increased myocardial contractility leading to a greater ventricular emptying during systole (30). The increased ventricular emptying (i.e., reduced ESV) is thought to offset the decline in EDV, which allows SV to be maintained or only slightly reduced during strenuous exercise. The increase in $\dot{Q}$ during the later stages of vigorous exercise is therefore thought to be related to the changes in heart rate and myocardial contractility (3, 18, 21, 25, 28, 30, 42).

We have observed that endurance athletes can increase their SV during incremental exercise in both the supine and upright positions in the face of reduced time for filling. These findings are similar to that reported by other investigators who evaluated ventricular responses to exercise in the upright position and supports the contention that endurance-trained athletes may make use of the Frank-Starling mechanism during the later stages of vigorous exercise (19, 31, 59, 62). For instance, Rerych et al. (44) reported that short term (6 month) endurance training leads to an enhanced ability to use the Frank-Starling mechanism throughout incremental exercise in the upright position (as evaluated by radionuclide ventriculography). Crawford et al. (10) evaluated changes in cardiac volumes in competitive marathon runners and non-competitive runners during upright exercise using two-dimensional echocardiography. They reported that the competitive endurance athletes had significantly greater increases in EDV throughout exercise in comparison to the non-competitive runners who exhibited greater increases in myocardial contractility (as evaluated by the SBP/ESV ratio). The authors postulated that the highly trained athletes may have an increased ability to make use of the Frank-Starling mechanism during incremental exercise. In the investigation of Crawford et al. (10) significant increases in EDV and SV were seen up to approximately 70% of maximum, despite the fact that the highest mean values for both EDV and SV (in both groups) were observed at maximal exercise (a finding that is quite similar to the present investigation).

Gledhill et al. (19) and Krip et al. (31) also reported that the SV of highly trained endurance athletes increased up to maximum without reaching a plateau, whereas the untrained participants' SV levelled off at approximately 40% of $\dot{V}O_2$max. Warburton et al. (59) also recently reported that the SV of endurance-trained male athletes continued to increase throughout incremental exercise in the upright position. Di Bello et al. (13) also reported that endurance athletes were able to increase their SV at peak exercise (as evaluated by Doppler echocardiography). This finding has also been shown in trained male prepubertal distance runners (46) (using Doppler echocardiography), and in highly trained female endurance athletes (61) (using the acetylene rebreathe method).

In the present investigation, SV continued to increase up until maximum exercise (but not significantly) in both the supine and upright positions. The increase in SV throughout exercise was largely the result of increases in EDV, since ESV only changed slightly throughout exercise. This was particularly evident at maximal exercise where ESV actually increased slightly in comparison to the previous work rate. Forward stepwise multiple regression revealed that EDV accounted for 93% of the variance in SV during incremental to maximal exercise in the supine position. During upright exercise, EDV accounted for 83% of the variance in SV. Therefore, in this subset of athletes, the Frank-Starling mechanism seems to be of great importance for the increase in SV throughout incremental exercise.

In the present investigation, the increase in EDV and SV was greatest during the earliest parts of exercise, which is similar to the findings of other investigators (10). The SV seemed to reach a slight plateau at around 130 to 150 beats·min^{-1} in both the supine and upright positions, but at maximal exercise there was another rise in SV (despite the slight increase in ESV). These results are quite similar to the findings of Gledhill and coworkers (19, 31, 57, 59, 62) and are indicative of the role the Frank-Starling mechanism plays throughout incremental exercise. Therefore, the increase in $\dot{Q}$ during submaximal and vigorous exercise seems to involve the combination of myocardial contractility, tachycardia and the Frank-Starling mechanism.

The relative contribution of each process to the increase in $\dot{Q}$ is hard to discern. Forward stepwise multiple regression for the prediction of $\dot{Q}$ from the variables heart rate, EDV, ESV, EF, and SBP/ESV revealed that heart rate and EDV were the strongest predictors of $\dot{Q}$ throughout incremental to maximum exercise in both the supine and upright positions. However, postural position had a large influence on the impact heart rate and EDV had on $\dot{Q}$. In the supine position, heart rate and EDV explained 63 and 33%, respectively, of the variance in $\dot{Q}$ throughout exercise. In the upright position, EDV explained 69% of the variance in $\dot{Q}$, in comparison to heart rate which explained 27% of the variance. In both positions, ESV and EF explained approximately 1% of the variance in $\dot{Q}$. During maximal exercise in the supine position, heart rate and EDV explained 56 and 39%, respectively, of the variance in maximal $\dot{Q}$. In the upright position, the relative roles of heart rate and EDV were reversed in comparison to supine exercise, with heart rate and EDV explaining 24 and 72%, respectively, of the variance in maximal $\dot{Q}$. Thus, postural position may affect the mechanism by which an increase in $\dot{Q}$ is achieved during incremental exercise especially maximal exercise (as discussed later). Also, the Frank-

Starling mechanism seems to be operative throughout incremental exercise.

Another interesting finding is that some normally active individuals have also been shown to increase their EDV and/or SV during maximal exercise. For instance, Goodman et al. (21) reported that normally active individuals were able to achieve progressively higher EDV during incremental exercise, with the highest values being attained during maximal exercise. Maximal exercise also resulted in a concomitant reduction in ESV and increase in the SBP/ESV ratio, which were greater than that achieved a lower work rate. The authors therefore postulated that an augmentation of preload (i.e., EDV) is primarily responsible for increasing SV during lower work rates, and myocardial contractility (as determined by the SBP/ESV and the lowered ESV) in conjunction with an increased preload allows for an augmentation in left ventricular performance during strenuous exercise. Also, Weibe et al. (61) recently revealed that both endurance-trained and untrained women were able to increase their SV during maximal exercise.

Myocardial Contractility

Ejection fraction, as calculated by SV/EDV, represents the percentage of blood in the ventricle at end-diastole that is ejected (29). In the present investigation, EF reached its peak value at approximately 90 to 100% of maximum exercise, a finding which is consistent in the literature (10, 21).

Ejection fraction is commonly used as a measure of myocardial performance. According to Robotham et al. (45) "A normal EF reflects the integrated system's ability to cope, under the conditions at the time of measurement, with abnormalities in preload, afterload, and/or contractility and still maintain an adequate cardiac output." Ejection fraction is often associated with myocardial contractility, however, it usefulness as a measure of myocardial contractility is limited, since it is both preload and afterload dependent (45). As Robotham and coworkers wrote (45) "Because it (EF) is clearly preload- and afterload-dependent, its usefulness as a measure of ventricular function is limited... From this perspective, EF becomes a measure, not of ventricular performance, but of the integrated system's performance in dealing with a pathologic process."

Therefore, the conclusion that an increase in EF during exercise indicates an increase in myocardial contractility is somewhat misleading.

The slope of the line V_O-ESBP (i.e., the end-systolic pressure volume relationship) (Figure 3.1) is a common measure of contractility and is termed E_{MAX}. The SBP/ESV ratio is a noninvasive index used to estimate the slope of the end-systolic pressure volume relationship. This is thought to be a better representation of myocardial contractility than EF since it is preload and afterload independent and little affected by heart rate (29, 45). However, caution must be taken when using this index of contractility, since it represents only one point within the pressure volume loop. As such, it is only an estimate of the slope of the end-systolic pressure volume relationship (i.e, E_{MAX}). It is therefore based on the assumption that the volume intercept (i.e., the unstressed volume) is zero, which is likely not the case (10).

In the present investigation, SBP/ESV increased from 2.47 to 4.66 $mmHg \cdot mL^{-1}$ during supine exercise, which is similar to that reported by Kanstrup et al. (29). There was a progressive increase in SBP/ESV throughout incremental exercise in both positions. As illustrated in Figures 13, 14, 21, and 22, the largest changes in in SBP/ESV were seen between the heart rates of 110 and 130 $beats \cdot min^{-1}$, thereafter the rate of increase was attenuated. These results indicate that in elite endurance trained athletes there are large increases in myocardial contractility during submaximal exercise, with smaller increments as maximal exercise is attained.

Oxygen Pulse and its Relationship with Stroke Volume during Incremental Exercise

According to the Fick equation, oxygen pulse, the ratio of (55) $\dot{V}O_2$ to heart rate, is a product of SV and arterio-venous oxygen difference ($a\text{-}\bar{v}DO_2$). Previous research has shown that submaximal SV may be estimated using the oxygen pulse (5). Therefore, the analysis of oxygen pulse may given further information regarding the SV response throughout incremental exercise. However, a paucity of information exists regarding the relationship between SV and oxygen pulse during incremental to maximum exercise in both the upright and supine positions. Bhambhani and coworkers (4, 5) revealed that oxygen pulse is directly related to SV during submaximal conditions. They therefore speculated that SV during submaximal conditions can be predicted from oxygen pulse.

As such, an increase in oxygen pulse during exercise conditions would be indicative of an increase in SV and $a\text{-}\bar{v}DO_2$. Warburton et al. (55) recently revealed that oxygen pulse may also be used to estimate SV during incremental to maximal exercise in highly trained endurance athletes. In their investigation, they found a linear increase in oxygen pulse, SV and $a\text{-}\bar{v}DO_2$ throughout incremental exercise in the upright position. The increase in oxygen pulse throughout incremental to maximum exercise was reflective of an increase in both $a\text{-}\bar{v}DO_2$ and SV (as determined by the acetylene rebreathe technique), contrary to Bhambhani et al. (4) who concluded that oxygen pulse is not related to $a\text{-}\bar{v}DO_2$. However, using stepwise forward multiple regression the authors reported that SV was the strongest predictor of oxygen pulse during incremental exercise (similar to Bhambhani and coworkers (4)). The present investigation, utilizing radionuclide ventriculography, also revealed a positive relationship between oxygen pulse, and SV and $a\text{-}\bar{v}DO_2$. Oxygen pulse continued to increase throughout exercise in both the upright and supine positions. The oxygen pulse response was slightly larger in the supine position than in the upright positions (Figure 20) (as was the SV response). These results indicate that oxygen pulse may be useful in the estimation of SV during exercise conditions in elite athletes in both the upright and supine positions. Also, an increase in oxygen pulse during incremental exercise is reflective of increases in both SV and $a\text{-}\bar{v}DO_2$. It is important to note, that the linear increase in oxygen pulse seemed to be strongly related to changes in $a\text{-}\bar{v}DO_2$, since the rate of increase in SV was not as great as that observed in oxygen pulse.

Diastolic Filling and Its Relationship with Changes in Preload

Systolic function or dysfunction was previously thought to be the major determinant of left ventricular performance. However, in recent years, the relative importance of diastolic function on left ventricular performance has been addressed (19, 24, 31, 35, 40, 59). Differences relating to diastolic function have been directly associated with the improvements in left ventricular performance brought about by endurance training (19, 31, 35, 59).

Diastolic function has been reported to be unchanged (14, 15, 22, 34, 37, 47, 48) or improved (7, 13, 19, 31, 33, 35, 41) after endurance training, with little or no effect on systolic function (14). Common indices of an enhanced diastolic function in endurance trained individuals include an increased early diastolic filling velocity and increased peak filling rate. Several investigators have revealed that the rate of diastolic filling exceeds that of systolic emptying (19, 31, 59, 61, 62) in endurance-trained athletes. Therefore, the major difference between endurance-trained athletes and their sedentary counterparts seems to be related to an enhanced capacity to utilize the Frank-Starling mechanism as reflected by an increased rate of diastolic filling and greater SV (19, 20, 31, 59, 61, 62). It is believed that this improvement in diastolic function allows for more complete filling during the later stages of vigorous exercise despite a reduction in heart rate (19, 20, 31, 59, 61, 62). In the present investigation, the rate of diastolic filling exceeded that of systolic emptying in both the supine and upright positions. These differences became more apparent as the exercise intensity increased and are indicative of the role the Frank-Starling mechanism played throughout incremental exercise (20).

Several mechanisms have been postulated for the increased rate of diastolic filling in endurance-trained athletes including an enhanced skeletal muscle pump, increased systemic venoconstriction, increased negative intrathoracic pressures as a result of increased ventilation, and increased blood volume (19, 20, 31, 46, 59, 61, 62). These adaptations all serve to increase preload and thus highlight the importance changes in preload have on left ventricular performance. However, the relative role of each mechanism on changes in preload and diastolic filling is difficult to determine.

Recent research has indicated that alterations in blood volume have a large impact on diastolic filling and the elevated myocardial performance of endurance athletes may be in part due to the training-induced expansion of blood volume (19, 31, 59). For instance, Krip et al. (31) examined the effects of changes in blood volume on cardiac function in endurance-trained cyclists and untrained individuals. Prior to acute changes in blood volume, the authors observed a significant improvement in SV, $\dot{Q}$, diastolic filling rate, blood volume, and systolic emptying rate in the athletes. Following a 500 mL withdrawal of whole blood in the endurance athletes and a 500 mL infusion of a plasma volume expander in the untrained athletes, the initial cardiovascular differences were minimized, especially with regards to diastolic filling and SV. The authors postulated that a large portion of the enhanced cardiovascular function of the endurance athletes is related to an enhanced blood volume and associated improvements in diastolic function.

In the present investigation, the changes in postural position allowed for a further evaluation of the impact changes in blood volume and preload have on diastolic function. For instance, the transition from upright to supine position resulted in an increased EDV reflecting an increase in preload (which was observed at rest and during each stage of exercise). The increased preload was associated with an enhanced diastolic filling rate throughout incremental exercise in the supine position. These results give further support to the contention that changes in blood volume will bring about an improvement in diastolic function. The relative importance of the other factors affecting preload cannot be directly determined from the present findings and requires further investigation. Coincident with an elevation in BV, endurance athletes may possess increased left ventricular internal cavity dimensions, increased negative left ventricular pressure, and/or enhanced myocardial compliance, which also serve to augment diastolic filling (8, 17, 20, 32). These adaptations may be related to the enhanced capacity of endurance athletes to utilize the Frank-Starling mechanism during exercise. However, it is important to note that there seems to be an upper limit to the capacity of the myocardium to fill, which may be related to the pericardium (as discussed later).

Supine versus Upright Exercise

Other investigators have examined the effects of changes in postural position on cardiovascular function in healthy individuals (11, 12, 38, 43). However, very little information exists regarding the cardiovascular response to changes in postural position in highly trained endurance athletes.

Postural changes from the supine position to the upright position will result in a net reduction in central BV and a concomitant reduction in venous return and SV. As such, the effective filling volume of the heart will be reduced in the transition from supine to upright exercise. In the present investigation, EDV and SV were consistently lower throughout incremental exercise in the upright positions, reflecting differences in the effective filling volume of the myocardium. However, the percent changes in SV from rest to maximum exercise were substantially larger than that observed during supine exercise.

Investigators have shown that there are minor changes in SV during incremental exercise in the supine position in healthy individuals (30). Thus, there seems to be a significantly greater capacity for diastolic filling in the upright position. That is, the myocardium may be near its limits for filling during supine exercise. This is supported by recent research which indicates that a large portion of the enhanced cardiovascular function of endurance athletes is related to their high blood volume (31, 59). However, this high blood volume may place the endurance athletes closer to their diastolic reserve capacity during upright exercise than their non-trained counterparts (31, 56, 59). For instance, further blood volume expansion in endurance athletes has been shown to lead to limited improvements in myocardial function (9, 26, 59). Whereas in untrained individuals there are substantial improvements in SV and $\dot{Q}$, in response to acute elevations in blood volume (31).

In the present investigation, the translocation of fluid to the myocardium as the result of postural changes would mimic acute changes in blood volume. In the upright position, there seems to be a greater reserve for diastolic filling as illustrated by the large gains in EDV and SV during incremental exercise. Whereas, the athletes, although still able to increase their EDV and SV, experienced smaller enhancements in EDV and SV during supine exercise compared to upright exercise. This is a similar finding to exercise in the water, where there is a large translocation of blood volume to the thoracic cavity and a consistent limitation in the elevations in EDV and SV during exercise conditions. Also, of interest was the finding that the athletes during supine exercise relied on chronotropic competence (i.e., heart rate) more than SV to increase maximal $\dot{Q}$, whereas during upright exercise the athletes relied more heavily on SV to increase maximal $\dot{Q}$.

Potential mechanisms for the limitation in the gains in EDV and SV during incremental exercise cannot be directly determined from the present investigation. It is possible that diastolic reserve is ultimately limited by the pericardium in these athletes. This is supported by research with heart failure patients (who also have a chronically elevated venous return), where the pericardium has a large effect on diastolic and systolic function (27). Therefore, as the volume of the myocardium is increased, the potential impact of the pericardium on ventricular filling may increase, thereby limiting the degree of ventricular filling. Further research is required to evaluate this hypothesis.

Myocardial Oxygen Consumption

No information exists regarding the measurement of $M\dot{V}O_2$ during supine and upright exercise in highly trained endurance athletes. Myocardial oxygen consumption was determined using both the RPP and the calculated PVA during resting and exercise conditions. Similar to the findings in healthy males (30), we observed a direct relationship between RPP and calculated $M\dot{V}O_2$ (Figure 23) in both the supine and upright positions. Postural position had no significant effect on $M\dot{V}O_2$ despite a significant effect of supine exercise on SW. The calculated resting $M\dot{V}O_2$ was 15.3 and 13.1 $mL \cdot 100\ g^{-1} \cdot min^{-1}$, respectively, during supine and upright exercise, which is similar to that reported in healthy individuals during supine exercise (30). Also, similar to that reported in healthy individuals (30), our athletes experienced an 4-fold increase in $M\dot{V}O_2$ in the supine position from rest to maximal exercise. In the upright position, the increase in $M\dot{V}O_2$ was slightly larger (i.e. 4.6-fold).

The efficiency of the myocardium during various loading conditions can be estimated using the formula of Suga and coworkers developed in canines (i.e., $0.38 \cdot SW/PVA$) (52). In the supine position, the calculated net efficiency was 27 ± 2% at rest and 30 ± 1% at maximal exercise, which is similar to that found by Kanstrup and coworkers in healthy individuals (30). The calculated net myocardial efficiency was also similar in the upright position at rest and during maximal exercise (i.e., 25 ± 2 and 30 ± 2%, respectively). These results highlight the capacity of the myocardium to maintain its efficiency from resting to exercise conditions.

Reasons for the Discrepancies in the Literature Regarding the Stroke Volume

Response to Exercise

The equivocal findings reported in the literature may be related to several factors. Research in this area is confounded by differences in measurement techniques, testing procedures, participant sample (i.e, normally active versus highly trained) and exercise intensity. Postural changes from the supine position to the upright position will result in a net reduction in central BV and a concomitant reduction in venous return and SV. Therefore, changes in SV during exercise may be minimized by supine exercise, where the loading conditions of the heart are vastly different and the impact of extra myocardial factors (such as venous return and/or the pericardium) may be extremely disparate. According to the results from the present investigation postural position will have a large impact on the magnitude of changes in cardiac volumes during incremental exercise. Furthermore, the mechanisms utilized to achieve these changes seem to be different, with supine exercise relying more on heart rate to increase $\dot{Q}$, and upright exercise relying more on EDV.

Also, many investigations have used measurement procedures, which are not suitable for maximal exercise conditions as reviewed by Warburton et al. (57, 58). The results obtained using these procedures may not accurately reflect the actual changes during maximal exercise. According to two recent reviews by Warburton et al. (57, 58) the acetylene rebreathe may be the best suited for maximal determinations of $\dot{Q}$ of the currently available non-invasive techniques. Several investigators using the acetylene rebreathe manouevre have revealed that the SV of highly trained endurance athletes increases throughout incremental to maximum exercise (19, 31, 57, 59, 61). It is essential to have accurate measures of SV during maximal exercise, because SV appears to level off at a submaximal exercise intensity and then reaches it highest level at maximal exercise (19, 31, 57, 59, 61). Many techniques (such as the carbon dioxide rebreathe method) can only take measures of SV and $\dot{Q}$ up to a submaximal exercise intensity. Given the tendency for SV to plateau and then increase during the latter stages of vigorous exercise, the maximal SV may be missed. Therefore, it is reasonable to argue that these techniques may be unable to measure true maximal values for SV (57, 58).

Several investigations that have achieved the highest SV values during maximal exercise have utilized supramaximal resistance settings to confirm the achievement of maximal values (19, 31, 57, 59, 61). These investigators utilized a acetylene rebreathe manouevre specifically modified for maximal exercise (57), which allowed for relatively quick determinations of both maximal and supramaximal SV. In the present investigation, we employed a supramaximal resistance setting to confirm the attainment of $\dot{V}O_2$max. However, our subjects were unable to maintain this resistance setting and/or remain still enough for radionculide scan to be successfully completed. As such, our maximal values for SV and $\dot{Q}$ may be under represented. Finally, many investigators have examined participants that were not highly trained and/or endurance trained for many years. The adaptations that arise from prolonged endurance training may be vastly different than those observed in moderately active individuals or individuals exposed to short term training.

Summary

In summary, exercise in the supine and upright positions results in a significant increase in $M\dot{V}O_2$ that is of a similar magnitude to that reported for normally active individuals. The myocardium is able to maintain a near optimal efficiency during exercise conditions. Highly trained endurance athletes are able to maintain and even increase their SV during incremental exercise in the upright and supine positions, despite a concomitant reduction in the time for diastolic filling. The observed increases in $\dot{Q}$ during incremental exercise in the supine and upright positions are related to increases in heart rate, myocardial contractility and the use of the Frank-Starling mechanism. Highly trained athletes make use of the Frank-Starling mechanism throughout incremental to maximum exercise in both the supine and upright positions. However, the potential increases in EDV and SV and therefore the reliance on the Frank-Starling mechanism seem to be greater in the upright position versus the supine position. It is likely that the chronic volume overload placed on the myocardium by athletes, who repeatedly exercise at a larger SV and $\dot{Q}$ than their non-trained counterparts, may lead to markedly different myocardial morphologic and functional adaptations. Some of the discrepancies in the literature regarding the SV response to exercise in athletes may be related to differences in postural position, testing procedures (e.g., exercise intensities), measurement techniques, and participant fitness levels.

Table 3.1. Baseline characteristics of participants (Mean ± SD).

Measure	Value
Age (yr)	26 ± 5
Mass (kg)	72 ± 6
$\dot{V}O_2$max (mL·kg^{-1}·min^{-1})	67.8 ± 3.9
$\dot{V}O_2$max (L·min^{-1})	4.84 ± 0.29
Blood Volume (mL)	5804 ± 749
Blood Volume (mL·kg^{-1})	82.4 ± 11.4
Plasma Volume (mL)	3307 ± 554
Plasma Volume (mL·kg^{-1})	46.9 ± 7.6
Red Cell Volume (mL)	2499 ± 235
Red Cell Volume (mL·kg^{-1})	35.5 ± 4.6

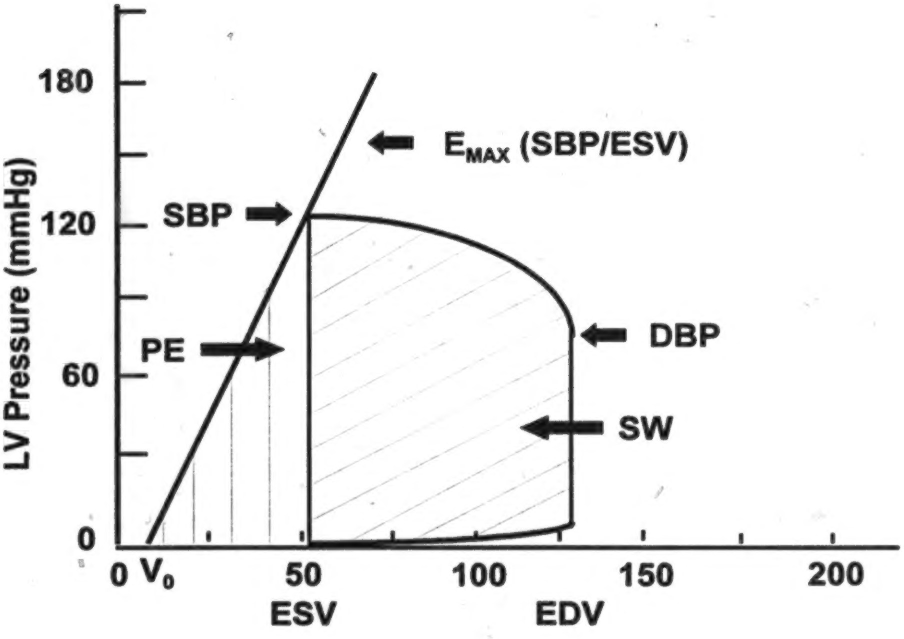
LV Pressure (mmHg)
180
120
60
0
0
V0
50
100
150
200
ESV
EDV
EMAX (SBP/ESV)
SBP
DBP
PE
SW

Figure 3.1. **Pressure-volume area during one cardiac cycle. E_{MAX}, myocardial contractility; SBP, systolic blood pressure; DBP, diastolic blood pressure; V_0, ventricular volume at zero pressure; ESV, end-systolic volume (mL); EDV, end-diastolic volume (mL); SW, stroke work (the area within the trapezium); PE, potential energy (the area within the triangle V_0-ESV-SBP).**

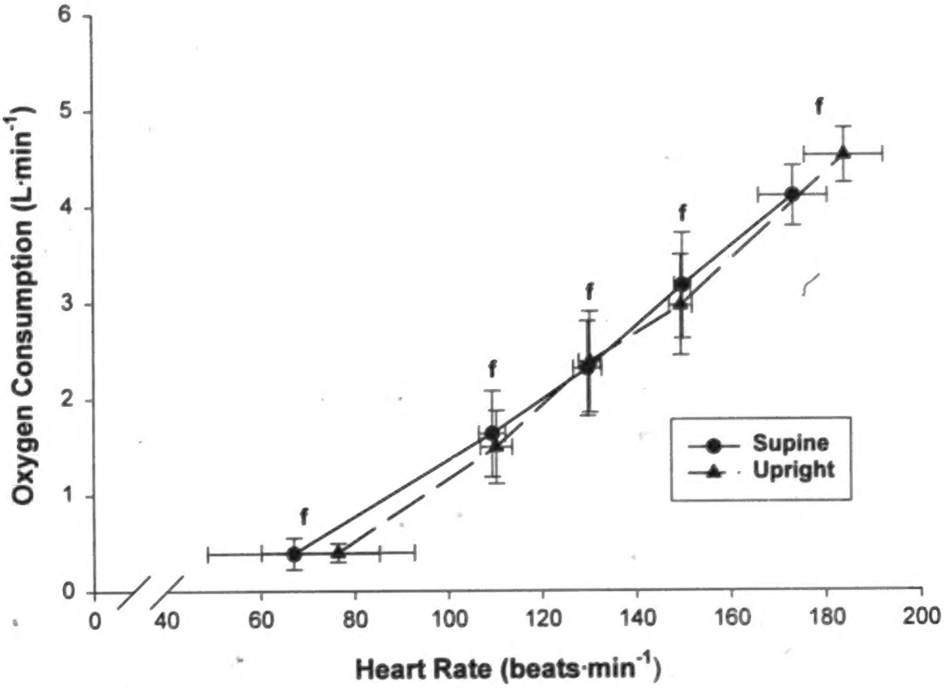

Figure 3.2. Oxygen consumption as a function of heart rate during incremental exercise in the supine and upright positions (Error Bars = SD). f, significantly different from all other heart rates ($p < 0.05$).

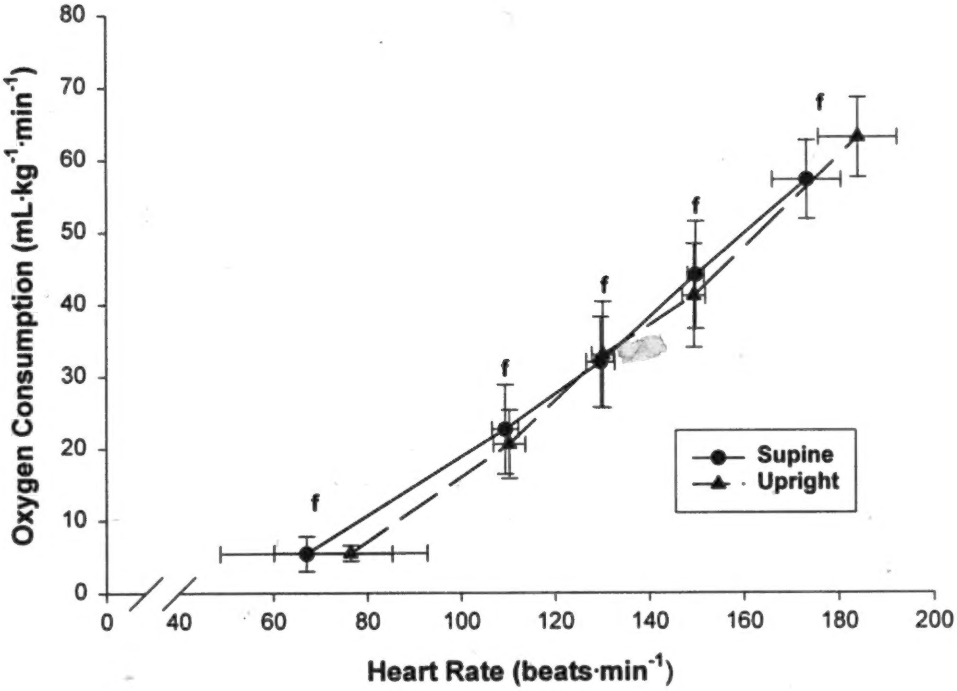

Figure 3.3. Relative oxygen consumption as a function of heart rate during incremental exercise in the supine and upright positions (Error Bars = SD). f, significantly different from all other heart rates ($p < 0.05$).

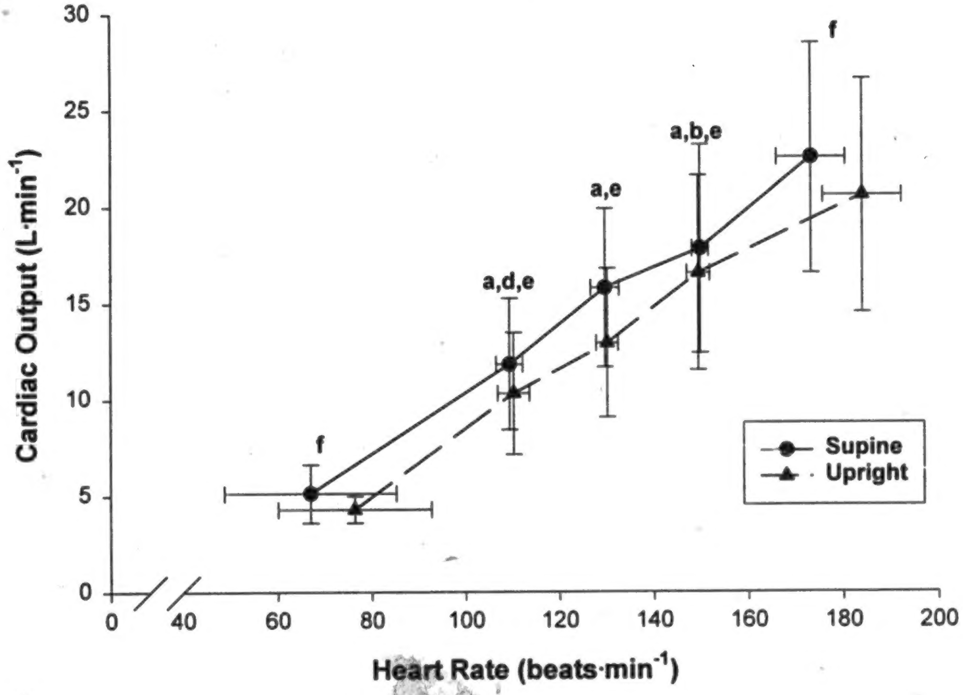

Figure 3.4. Cardiac output response to incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates ($p < 0.05$).

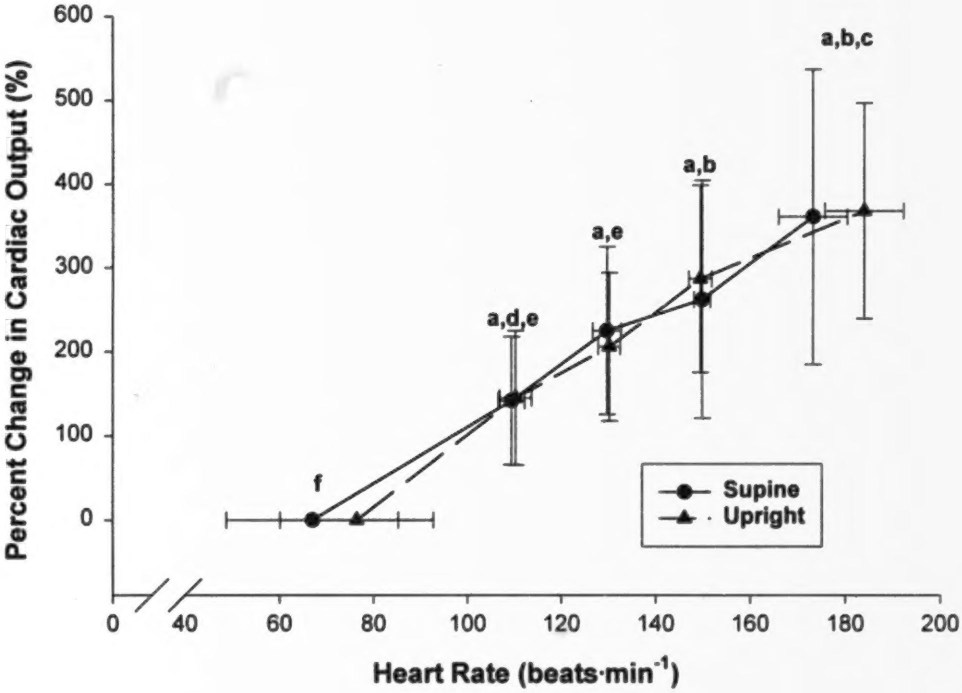

Figure 3.5. Percent changes in cardiac output during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates ($p < 0.05$).

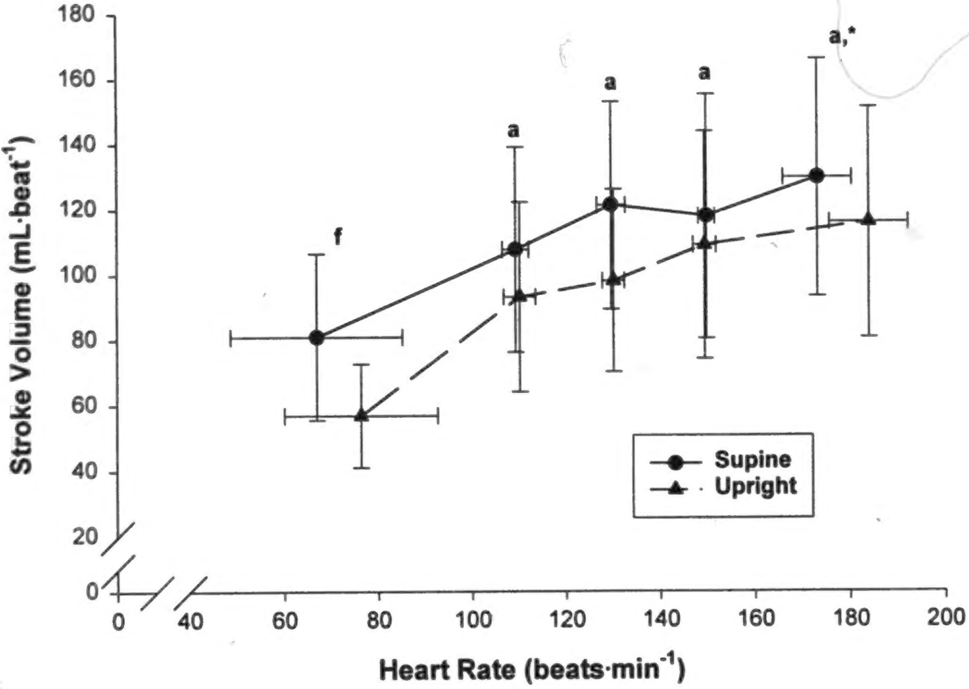

Figure 3.6. Stroke volume response to incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; f, significantly different from all other heart rates; *, significant difference between supine and upright exercise ($p < 0.05$).

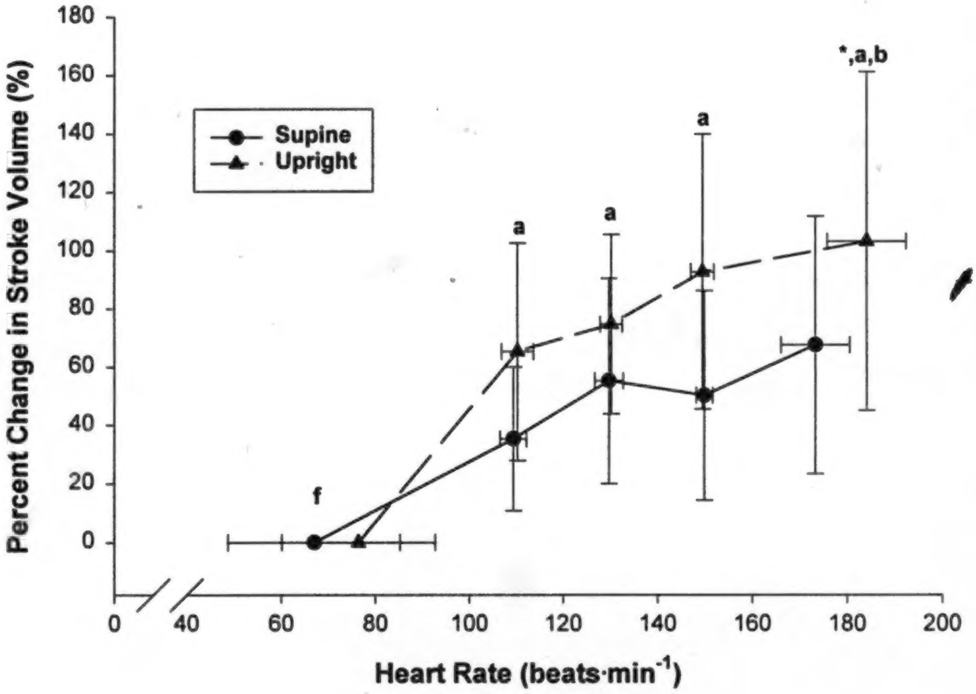

Figure 3.7. Percent change in stroke volume during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; f, significantly different from all other heart rates; *, significant difference between supine and upright exercise ($p < 0.05$).

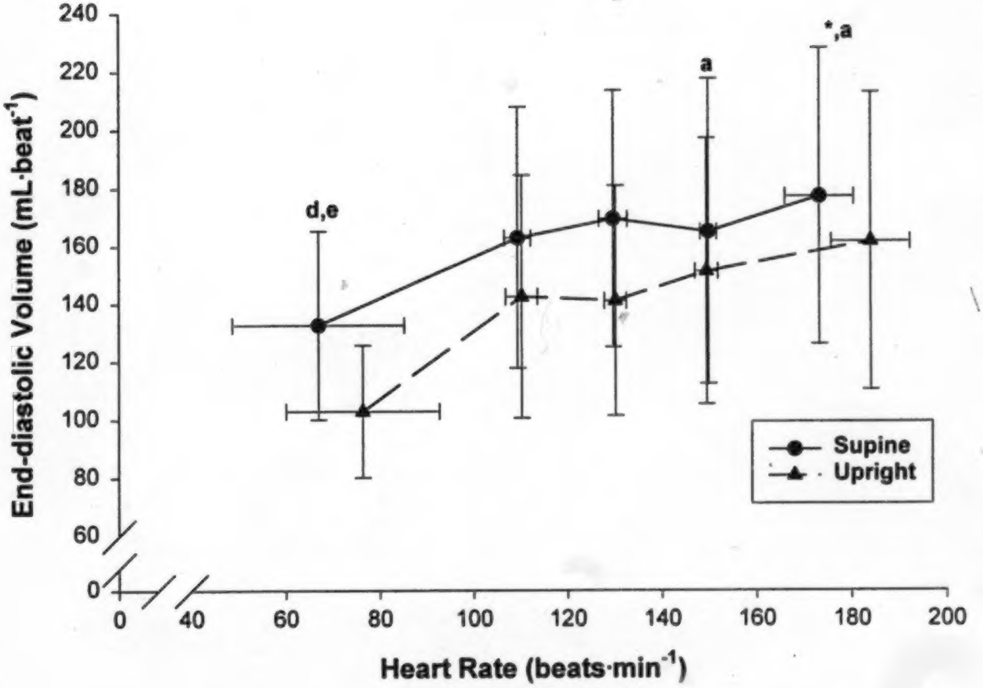

Figure 3.8. End-diastolic volume response to incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; *, significant difference between supine and upright exercise ($p < 0.05$).

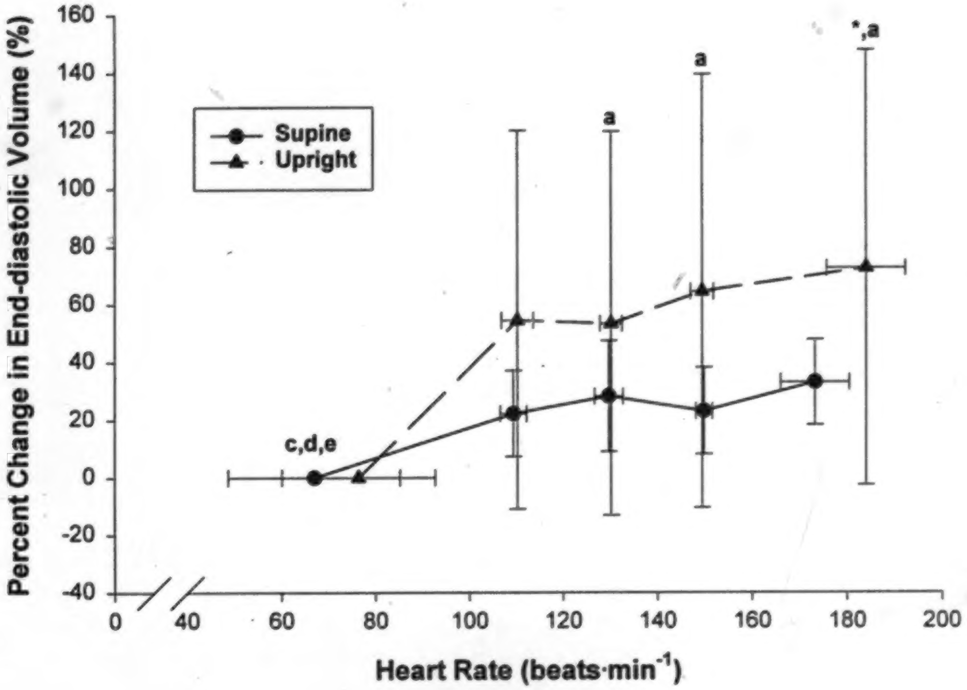

Figure 3.9. Percent change in end-diastolic volume during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates; *, significant difference between supine and upright exercise ($p < 0.05$).

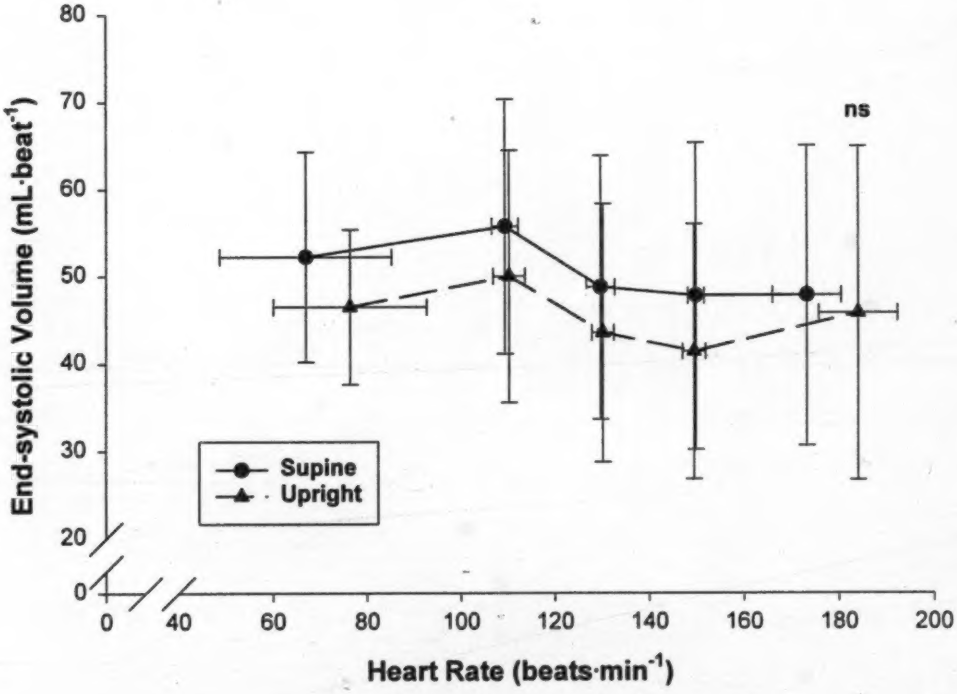

Figure 3.10. End-systolic volume response to incremental exercise in the supine and upright positions (Error Bars =SD). ns, no significant changes throughout incremental exercise ($p < 0.05$).

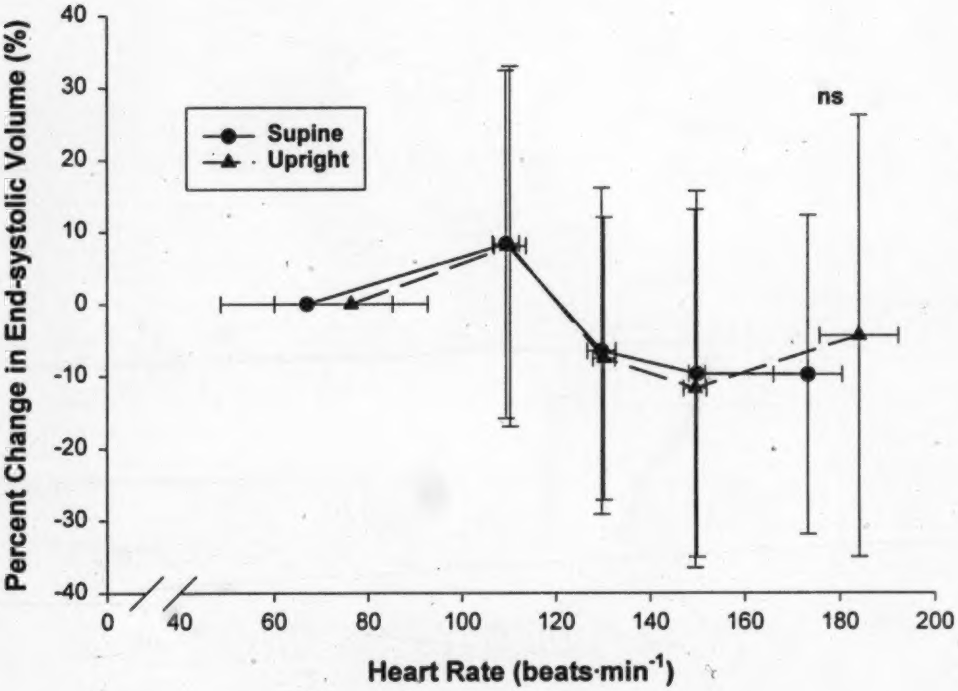

Figure 3.11. Percent change in end-systolic volume during incremental exercise in the supine and upright positions (Error Bars =SD). ns, no significant change throughout incremental exercise ($p < 0.05$).

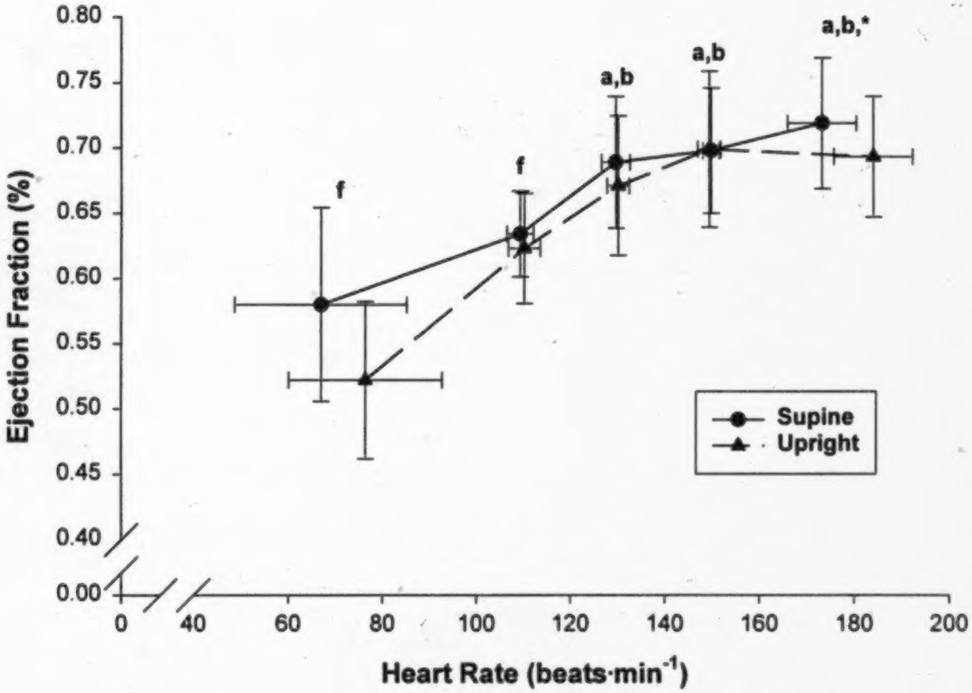

Figure 3.12. Ejection fraction response to incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; f, significantly different from all other heart rates; *, significant difference between supine and upright exercise ($p < 0.05$).

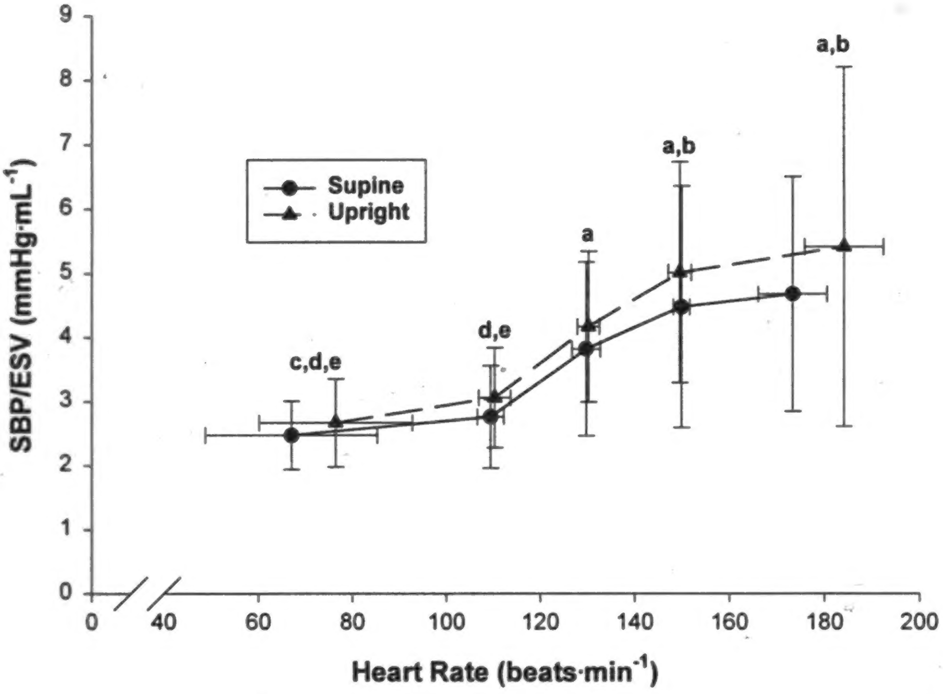

Figure 3.13. Systolic blood pressure to end-systolic volume ratio response to incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise ($p < 0.05$).

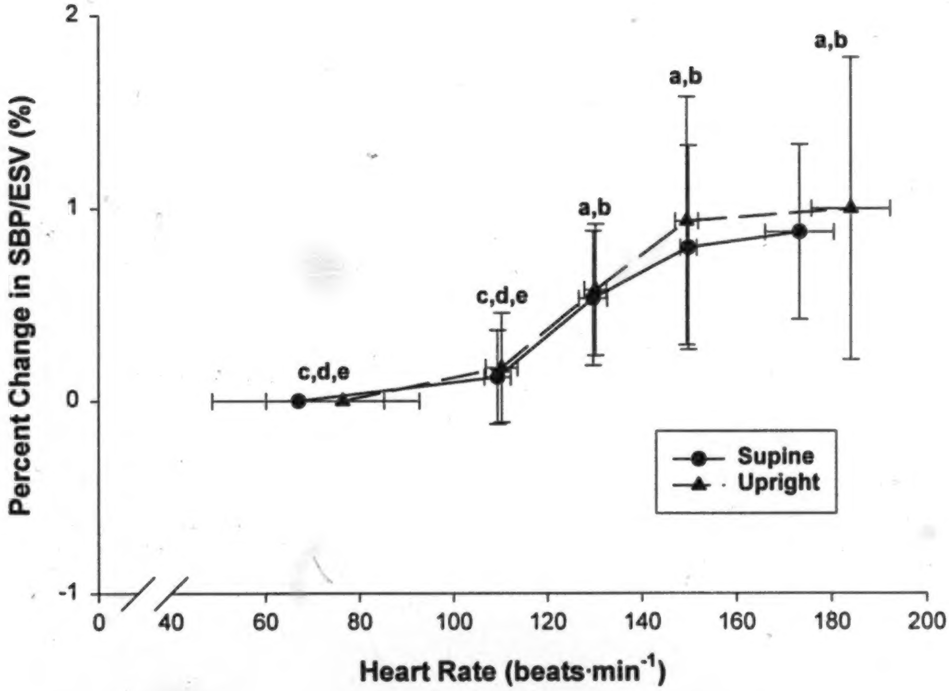

Figure 3.14. Percent change in systolic blood pressure to end-systolic volume ratio during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise ($p < 0.05$).

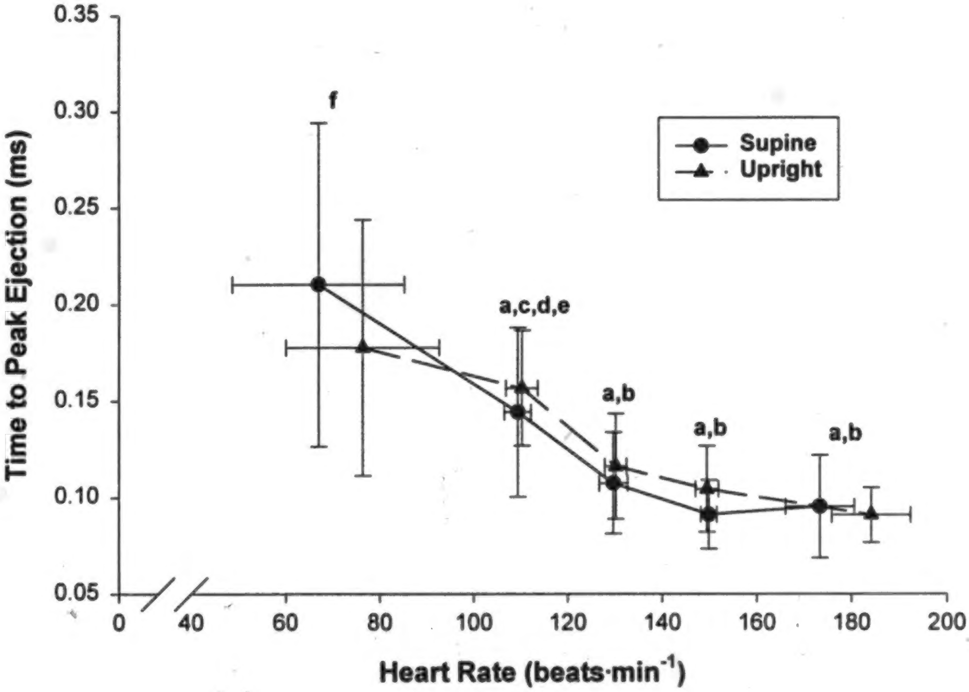

Figure 3.15. Time to peak ejection during incremental exercise in the supine and upright positions (Error Bars =SD).
a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates ($p < 0.05$).

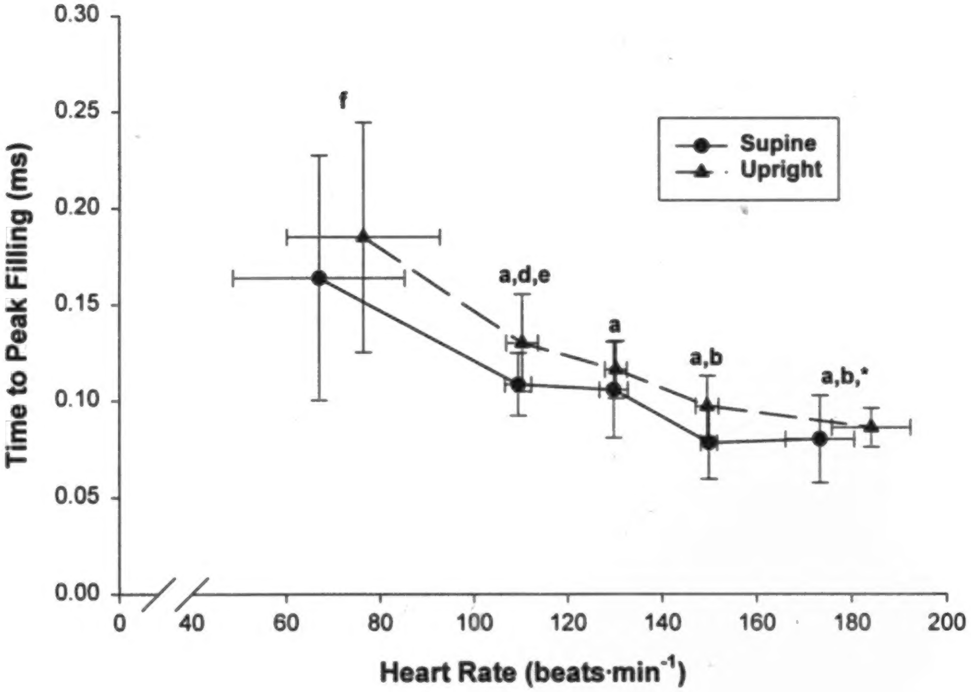

Figure 3.16. Time to peak filling during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates; *, significant difference between supine and upright positions ($p < 0.05$).

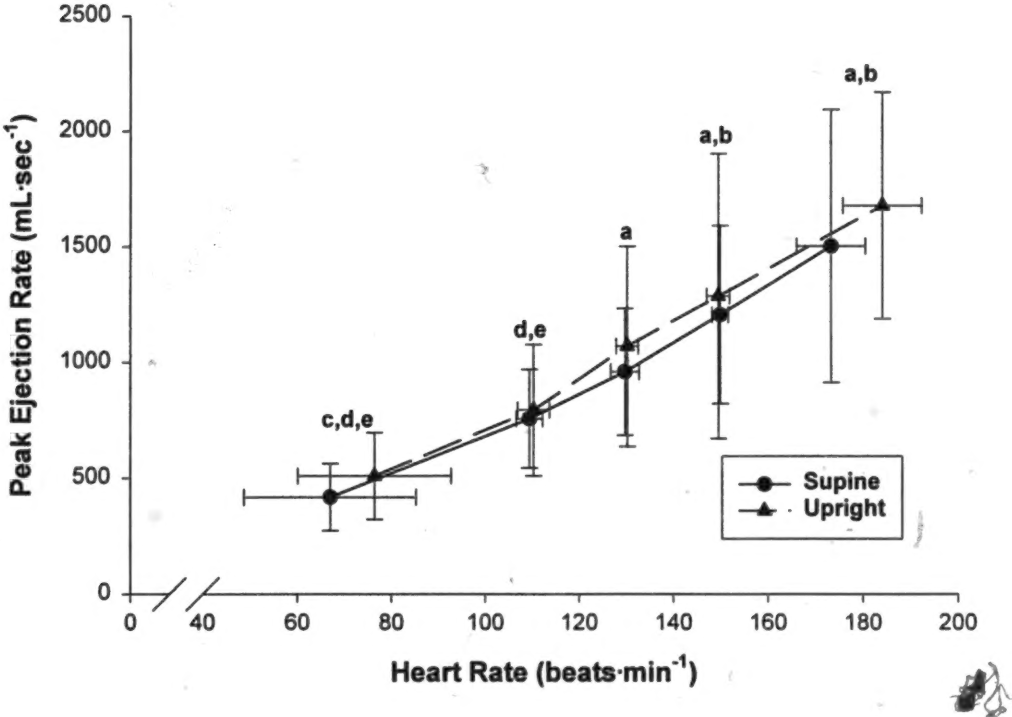

Figure 3.17. Peak ejection rate during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise ($p < 0.05$).

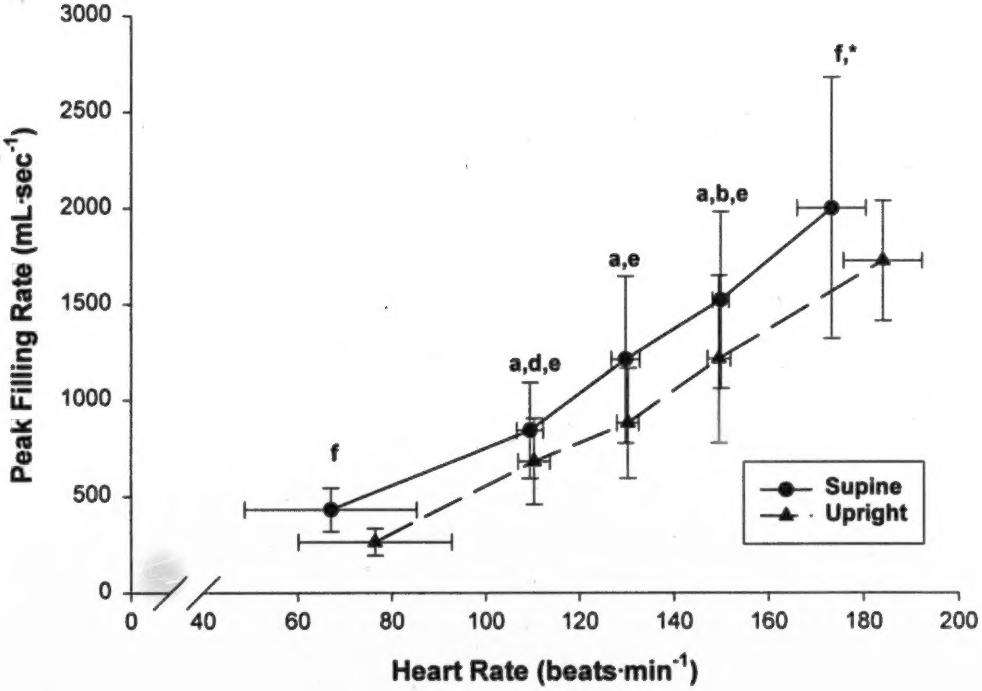

Figure 3.18. Peak filling rate during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates; *, significant difference between supine and upright positions ($p < 0.05$).

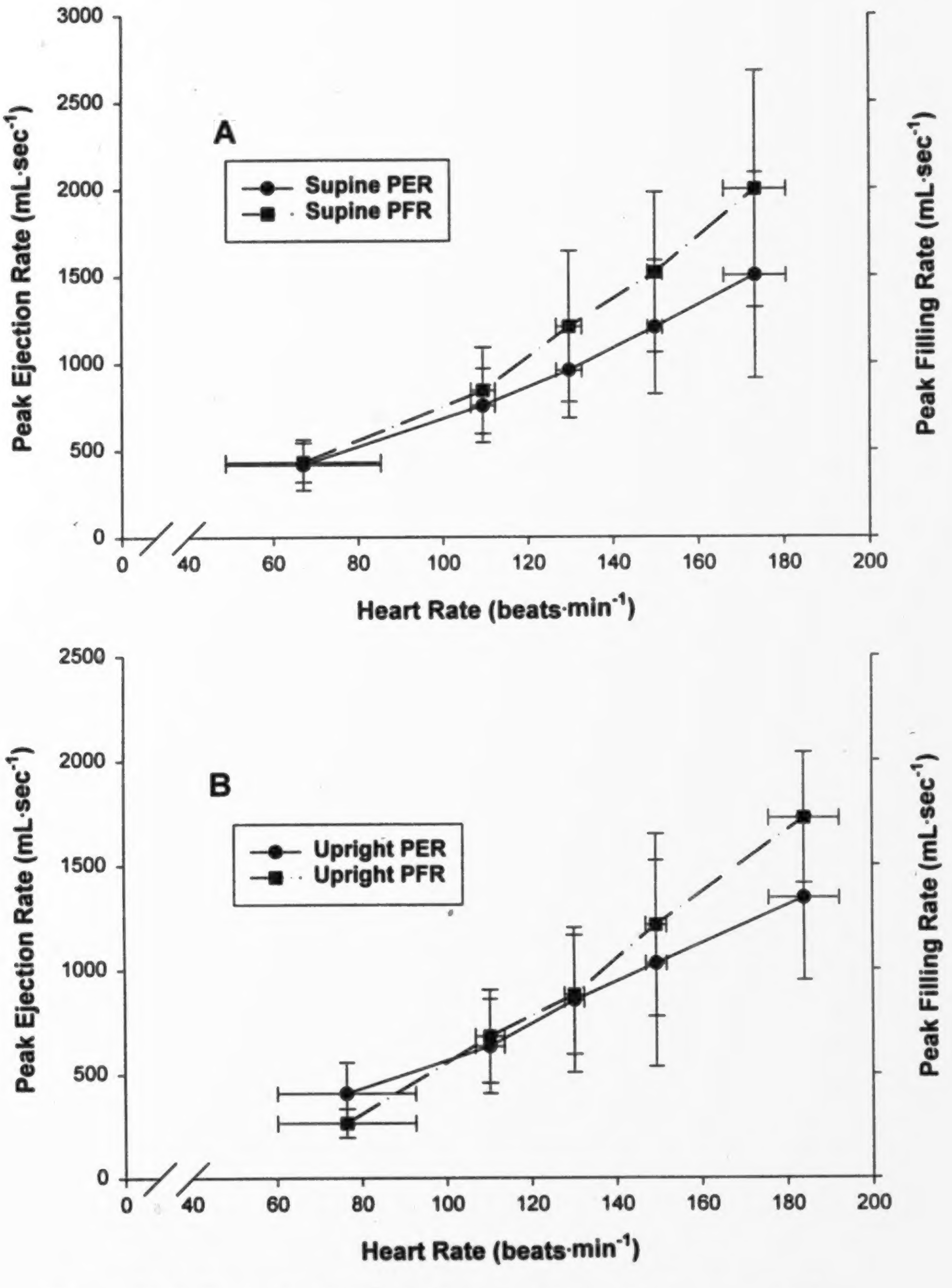

Figure 3.19. Peak ejection and filling rates during incremental exercise in the supine (A) and upright (B) positions (Error Bars =SD).

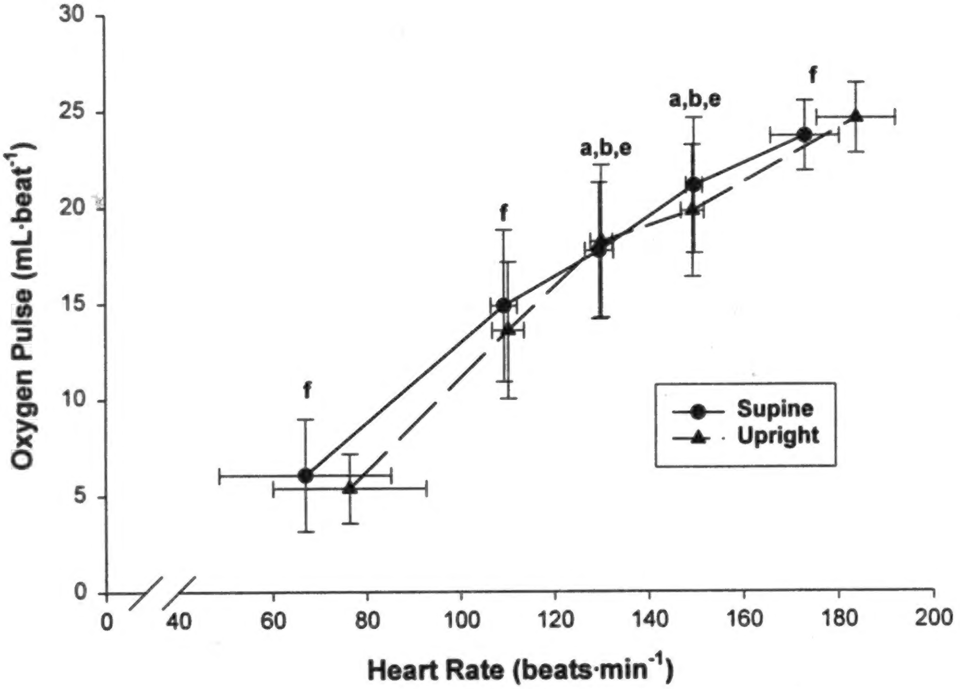

Figure 3.20. Oxygen pulse during incremental exercise in the supine and upright positions (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates ($p < 0.05$).

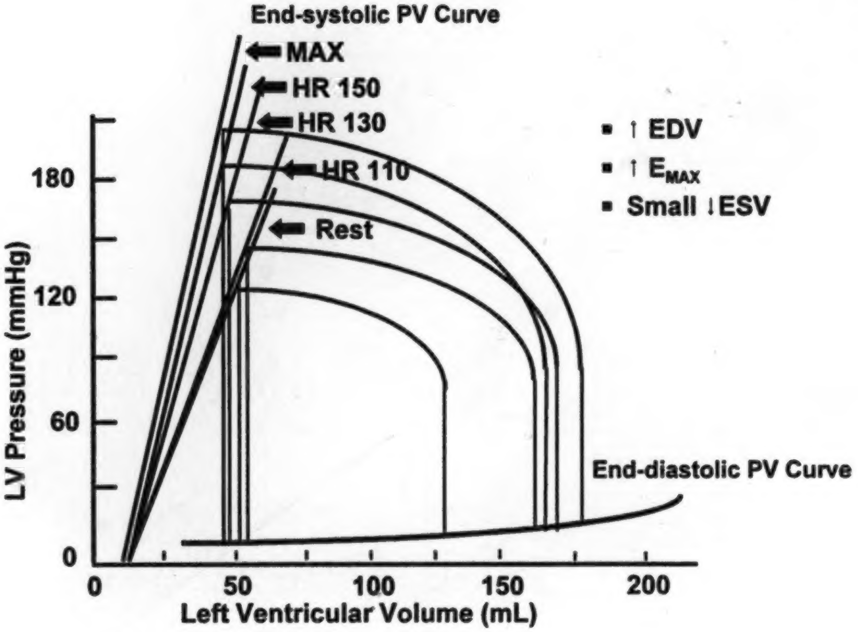

Figure 3.21. Alterations in the pressure-volume relationships throughout incremental exercise in the supine position. Slope of the end-systolic pressure volume line refers to E_{MAX} (calculated as systolic blood pressure divided by end-systolic volume). The end-diastolic pressure volume curve and the zero intercept (V_0) of the end-systolic pressure volume line are both theoretical.

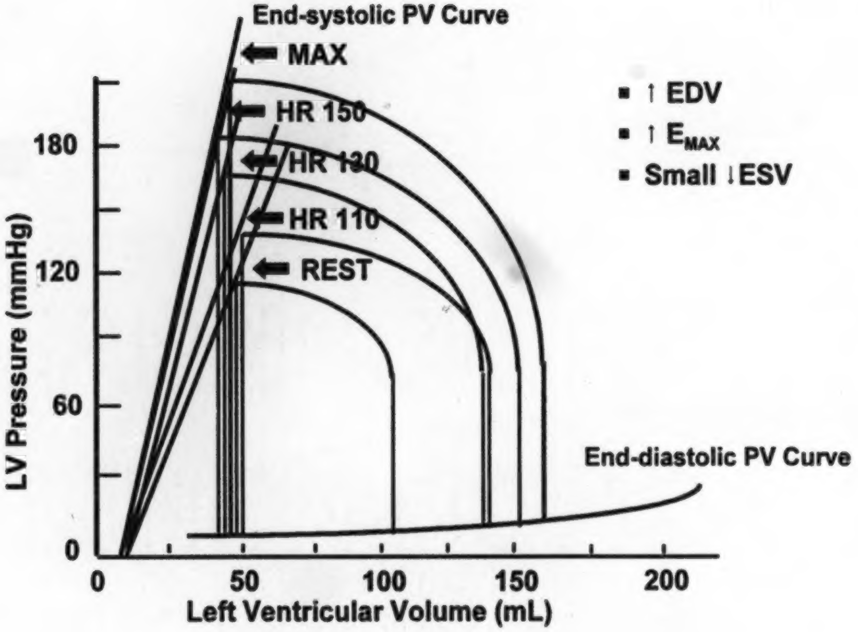

Figure 3.22. Alterations in the pressure-volume relationships throughout incremental exercise in the upright position. Slope of the end-systolic pressure volume line refers to E_{MAX} (calculated as systolic blood pressure divided by end-systolic volume). The end-diastolic pressure volume curve and the zero intercept (V_0) of the end-systolic pressure volume line are both theoretical.

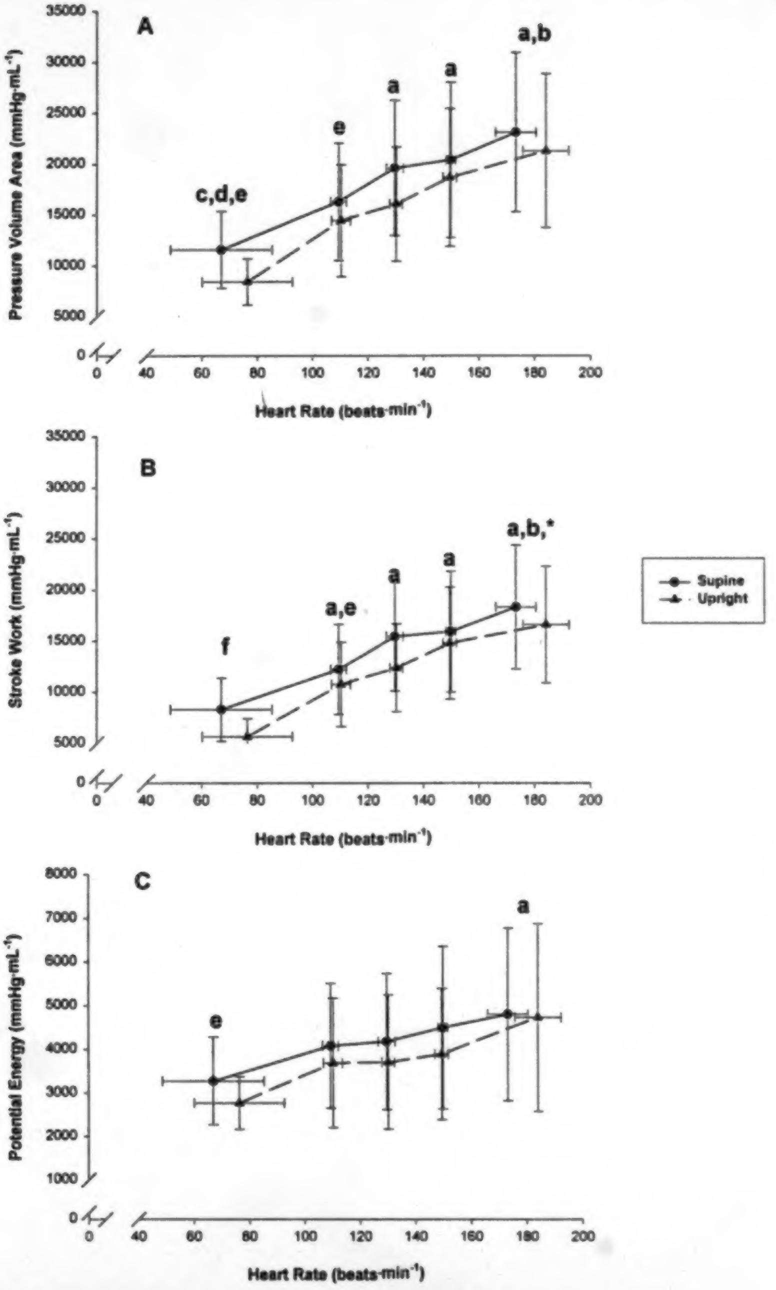

Figure 3.23. Pressure-volume area (A), stroke work (B), and potential energy (C) during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other heart rates; *, significant difference between the supine and upright positions ($p < 0.05$).

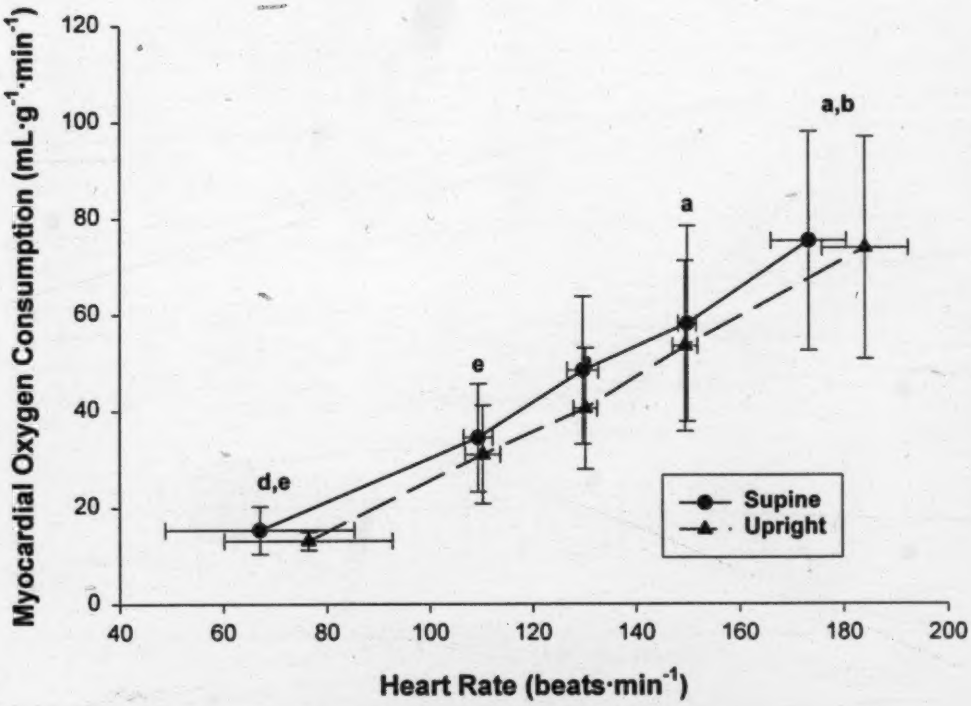

Figure 3.24. Calculated myocardial oxygen consumption during incremental exercise in the supine and upright positions (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise ($p < 0.05$).

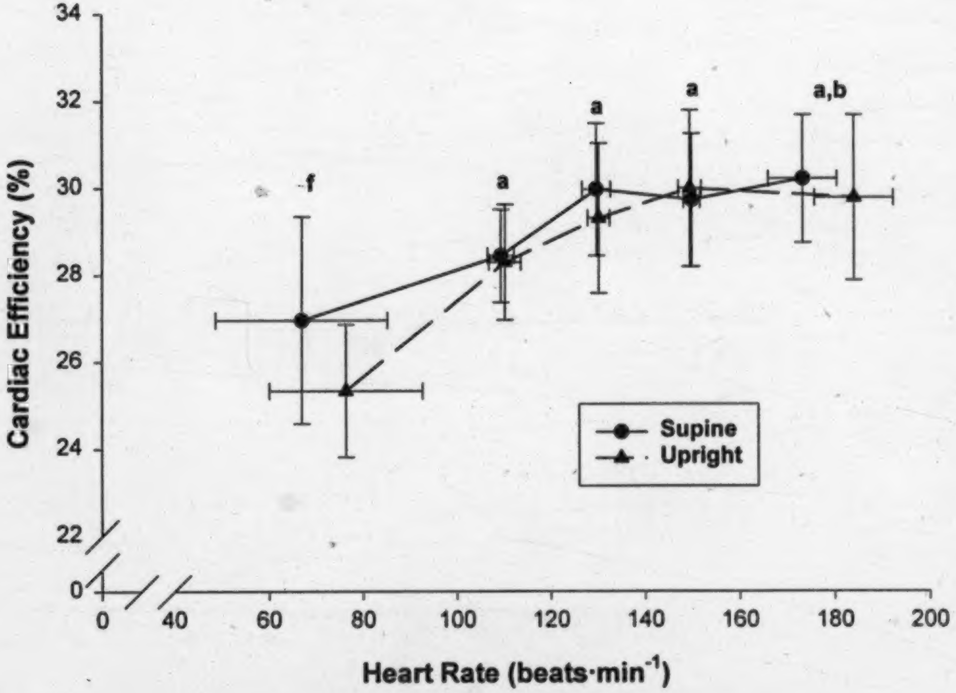

Figure 3.25. Myocardial efficiency during incremental exercise in the supine and upright positions (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; f, significantly different from all other staged heart rates ($p < 0.05$).

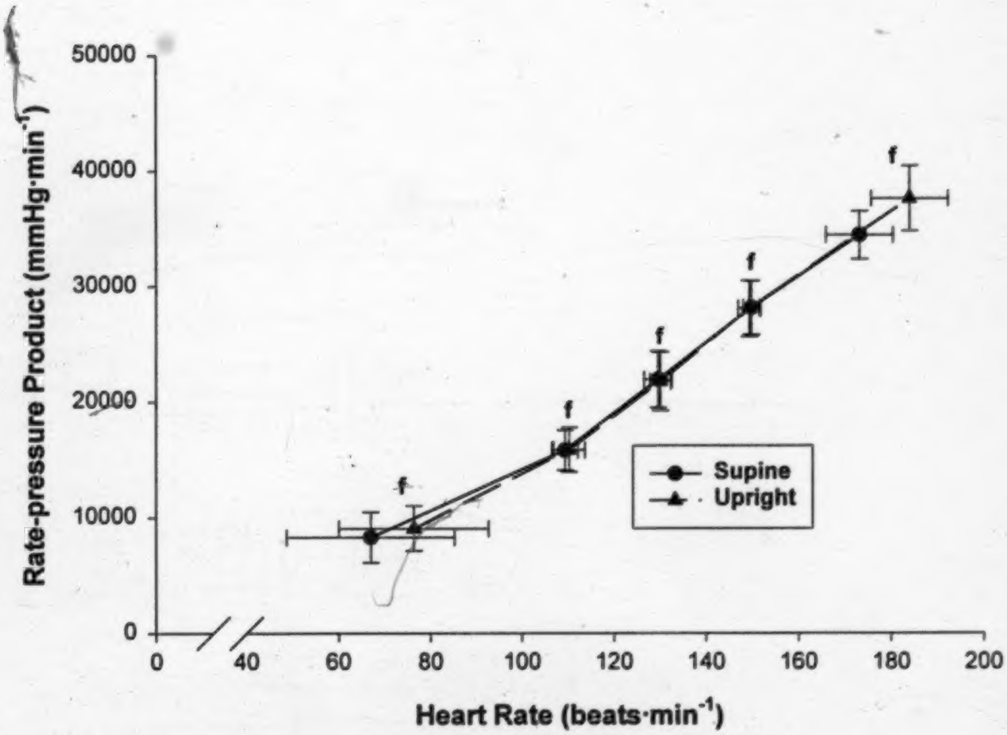

Figure 3.26. Rate-pressure product during incremental exercise in the supine and upright positions (Error Bars = SD). f, significant difference between all staged heart rates ($p < 0.05$).

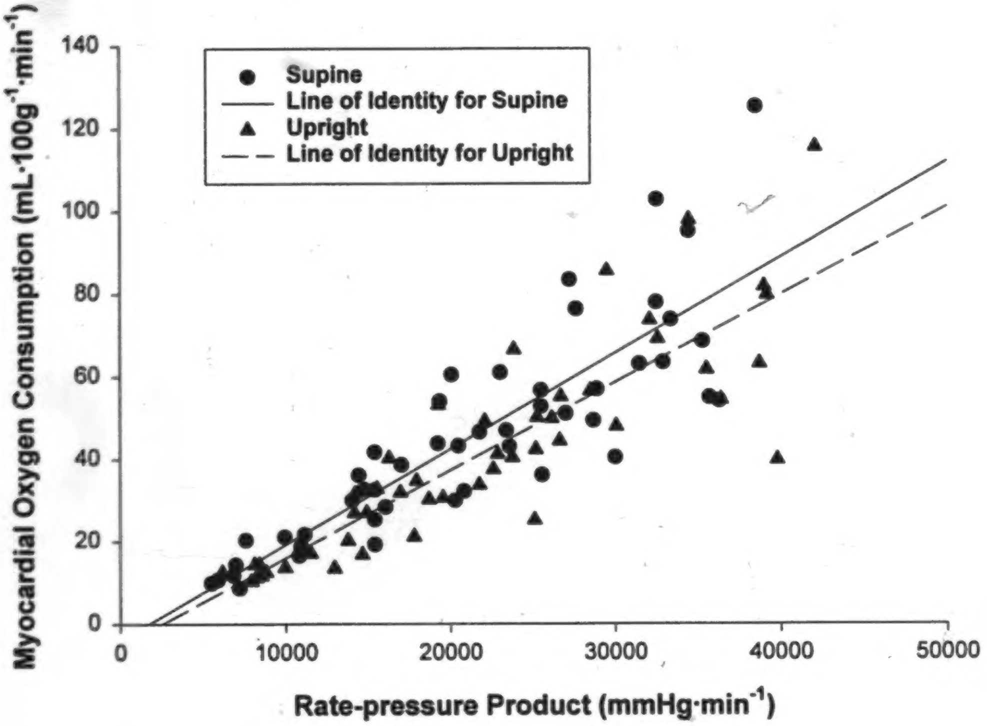

Figure 3.27. Relationship between rate-pressure product and calculated myocardial oxygen consumption during supine and upright exercise.

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CHAPTER FOUR

Effects of Continuous versus Interval Training on Blood Volume, Left Ventricular Morphology and Function, and Volume-Regulatory Hormones

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Abstract

Objective: *To monitor changes in blood volume (BV), hormones involved in BV regulation, maximal aerobic power (VO$_2$max) and left ventricular (LV) morphology and function as a result of two different forms of endurance training.* ***Methods:*** *Participants (N = 24, Age ± SD = 30 ± 4 yr, VO$_2$max = 39 ± 7 mL·kg^{-1}·min^{-1}) were matched (for body mass and VO$_2$max) and randomly assigned to control (CTRL; N = 8), continuous training (CONT; N = 8) or interval training (INT; N = 8). The training groups exercised on a cycle ergometer 3 days/wk for 12 wks. Continuous training consisted of cycling at 1% below anaerobic threshold for 30-48 min/day. The INT group exercised using 2 min work:2 min recovery bouts (at 90% and 40% VO$_2$max, respectively) for a duration that allowed an equivalent work output to CONT. Measures of VO$_2$max (metabolic cart) and LV morphology (M mode echocardiography) and function (radionuclide ventriculography) were taken during baseline (PRE), at mid-training (MID) and at the end of training (POST). Measures of BV (Evans Blue) and hormones involved in BV regulation (i.e., angiotensin II, aldosterone, and atrial-natriuretic peptide) were taken at PRE, wk one, wk three, MID, wk nine and POST in both training groups.* ***Results:*** *BV was increased as a result of both CONT and INT throughout training ($p < 0.05$). The mean percent BV expansion (across all weeks of training) was greater in the CONT group versus the INT group (11.2 ± 7.2 vs 7.9 ± 5.3%, $p < 0.05$). The mean percent PV expansion was also greater in the CONT group (11.4 ± 7.1 vs 7.1 ± 6.9%, $p < 0.05$). VO$_2$max increased as a result of both CONT and INT (21.4 ± 12.8% versus 16.7 ± 10.9%, respectively, $p < 0.05$), but was not significantly different between CONT and INT. There was a significant relationship between percent changes in VO$_2$max and percent changes in BV and PV ($r = 0.63$ and $r = 073$, respectively, $p < 0.05$). No significant difference existed between groups with regards to LVIDd, VST, PWT, and LVM. No significant changes occurred in resting concentrations of aldosterone and atrial-natriuretic peptide. Angiotensin II was significantly elevated after one week of CONT and INT training and thereafter returned to baseline values.* ***Conclusions:*** *Changes in BV account for a large portion of the enhancement in VO$_2$max after CONT and INT. Twelve weeks of CONT training results in a significantly larger improvement in BV in comparison to INT, which may account for the slightly enhanced VO$_2$max of CONT. The early increase in BV is associated with an increased concentration of angiotension II. Twelve weeks of CONT and/or INT does not provide a sufficient stimulus for alterations in LV morphology.*

INTRODUCTION

Extensive research has been conducted examining the central and peripheral adaptations that occur as a result of endurance training. Endurance athletes display characteristic improvements in cardiovascular function including an increased cardiac output ($\dot{Q}$), stroke volume (SV) and maximal aerobic power ($\dot{V}O_2$max) (33, 52). Coincident with this improved cardiovascular function is an expanded blood volume (BV) (hypervolemia) (11, 52), which is approximately 15% larger than untrained individuals (as previously discussed in Chapter Two).

Increases in BV are associated with concomitant increases in SV and cardiac output $\dot{Q}$. This relationship occurs because hypervolemia will lead to an enhanced venous return, which allows for an increased ventricular filling and end-diastolic volume (EDV). Investigators have postulated that a large portion of the enhanced cardiovascular function of endurance athletes is merely a passive response to their larger BV (33, 52, 104, 106, 107). However, a great deal of controversy exists regarding the role BV plays in the enhanced cardiovascular function of endurance athletes (47, 106).

A series of cross-sectional and longitudinal investigations have examined the differences in BV between endurance trained and untrained individuals (1, 4, 14, 33, 40, 51, 52, 76, 98). These investigations revealed that endurance training results in a significantly larger BV and an improved cardiovascular performance. The majority of the longitudinal investigations have examined the effects of continuous training, at an intensity of approximately 70-80% $\dot{V}O_2$max. This form of training may result in significant myocardial adaptations (including morphologic and functional changes), owing to exercising for prolonged periods of time at high $\dot{Q}$ and perhaps the exercise-induced increase in BV. However, very little is known about the alterations in BV and myocardial morphology and function that occur after interval training. It is also unclear the effects of different aerobic training programs on hormones involved in blood volume regulation. Therefore, it was important to gain a knowledge of the adaptations in BV, myocardial morphology and function, and the volume-regulatory hormones that occur as a result of two different forms of endurance training. This knowledge is not only important for exercise performance and healthy living, but is essential for practitioners dealing with congestive heart failure patients where improvements in aerobic fitness are desirable, but alterations in left ventricular (LV) morphology and increase~~s~~ in BV may not be.

Controversy also exists regarding whether continuous or interval endurance training will lead to greater improvements in $\dot{V}O_2$max (15, 19, 36, 58, 71, 78). Gledhill and coworkers have previously shown that BV plays a large role in augmenting $\dot{V}O_2$max and cardiovascular performance (52, 107). Elevations in BV are directly related to the intensity and duration of the activity, with the latter playing the dominant role (refer to review of literature). We therefore hypothesized that continuous training may lead to a greater elevation in BV. We speculated that as a result of the elevated BV, $\dot{V}O_2$max would also be increased to a greater extent after continuous training.

Therefore, the purpose of this investigation was to monitor changes in BV, volume-regulatory hormones, $\dot{V}O_2$max, and left ventricular (LV) morphology and function as a result of two different forms of endurance training.

METHODOLOGY

Participants

Twenty-five normally active males volunteered for participation in this investigation. Participants were recruited from the general population of the University of Alberta and the city of Edmonton, using previously approved recruitment notices. Participants were fully informed of the protocol and the time commitment of the investigation. All subjects participated in this investigation with informed consent and approval of the university's Health Sciences Research Ethics panel. Inclusion criteria included normally active male participants aged 18 to 40 years with a maximal aerobic capacity of less than 55 $mL \cdot kg^{-1} \cdot min^{-1}$. Exclusion criteria included: 1) engagement in a regimented endurance training program within the previous 6 months, 2) abnormal blood pressure or ECG responses during exercise testing, 3) uncontrolled systemic hypertension (e.g. BP $\geq$160/90), 4) respiratory limitation due to documented lung disease, 5) participation in another research investigation within 30 days, 6) any known myocardial disease, 7) presence of risk factors for coronary artery disease, and/or 8) an uninterpretable resting ECG. Based on these entrance requirements one participant was not permitted to engage in the investigation, due to previous heart disease (as evaluated by a cardiologist using echocardiography). Baseline characteristics of the participants are shown in Table 4.1. Two participants in the interval training group and one in the continuous training group dropped out after week six, owing to conflicts with their working schedule. One participant was injured after week nine of continuous training. This participant was able to return after a period of recovery. However, because of the delay, the participant's data for week 12 was excluded from the reported means.

Study Protocol

The basic design for this investigation was a 3-arm parallel design (group x measurement period) randomized, controlled investigation. Participants were matched (for body mass and aerobic fitness) and randomly assigned to control (usual activities), continuous aerobic training or interval aerobic training conditions. The continuous and interval training groups were evaluated for all measurements at baseline, and weeks six and 12. The control group was evaluated for all measurements at baseline and at week 12. The endpoints of BV and basal levels of volume-regulating hormones were assessed at baseline, and after weeks one, three, six, nine and 12 in the continuous and interval training groups. The control group had their BV and basal levels of volume-regulating hormones measured at baseline and after 12 weeks of normal activity.

This investigation required the participants in the continuous or interval training groups to participate in two pre-training test days, two mid-training test days, two post-training test days and 12 weeks of aerobic training. All training was conducted at the dedicated exercise facilities located in the Van Vliet Physical Education Centre. All testing was conducted at the exercise stress laboratory in the Division of Cardiology at the University of Alberta Hospital. The control group was asked to refrain from engaging in an exercise program and to continue their usual physical activities.

Pre-training Sessions

Participants were instructed to refrain from physical activity and the consumption of caffeinated beverages 24 hrs prior to the test days. Participants were required to report to the Division of Cardiology on Day 1 for resting BV and resting concentrations of the volume-regulatory hormones (as described later). After the resting blood measures were taken, the participants performed an incremental to maximum cycle ergometer exercise in the semi-recumbent position to assess LV function using radionuclide ventriculography (as discussed later). After a minimal 24 hour period of inactivity the participants were required to report to the Adult Echocardiography laboratory at the University of Alberta Hospital for the baseline assessment of LV morphology and function (using 2-dimensional echocardiography and Doppler echocardiography, respectively).

Randomization Procedures

Immediately after the last pre-testing session, the participants were stratified according to their fitness levels and body mass. The participants were then randomly assigned to either continuous training, interval training or control (usual activities) groups using computer-generated random sequencing. Randomization was conducted by a person who was unfamiliar with the hypotheses of this investigation.

Training Period

The subjects were randomly assigned to either continuous training, interval training, or control groups. Participants were required to train for 3 days·week^{-1} for 12 weeks on a Monark cycle ergometer (Model 818, Stockholm, Sweden). All conditioning days were monitored by personnel who were trained to adjust the work rates according to heart rate (as discussed later). Each training day began with a standardized 5 min warm-up period, consisting of the participant exercising at 30% of peak power output at a pedalling cadence of 80 revs·min^{-1}.

Continuous Training

Aerobic training was performed on a cycle ergometer with the work rate set individually at 1% below the participant's anaerobic threshold for 30-48 min/day based on the pre-test training exercise test. Anaerobic threshold was assessed using the breakaway point in the relationship between minute ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}CO_2$) (i.e., $\dot{V}_E/\dot{V}CO_2$) (as discussed later). The duration of training was 30 min for the first two weeks of training, 36 min for weeks three to four, 42 min for weeks five to six, and 48 min for weeks seven to 12. Participants were instructed to maintain a pedalling cadence of 80 revs·min^{-1}. Each training week consisted of three days of continuous training on intermittent days. Blood volume and the volume-regulating hormones were measured at weeks one, three, six, nine and 12 of training (as described later).

On weeks six and 12, participants participated in three days of continuous training (as outlined above) and then repeated the testing done on the pre-training days. Individual work rates were adjusted after mid-training to account for improvements in aerobic fitness and skeletal strength. During the remainder of the training regimen the work rates were adjusted according to a heart rate range to reflect changes in the participants' fitness. This heart rate range was based on the mean heart rate throughout continuous training from minutes 10 to 30 during the first week of training. A range of ±5% was calculated and if the participants fell outside of this range after 10 to 20 min of training, the resistance setting was adjusted accordingly (±2.5%) (36). The average work output per session increased from 277348 ± 94453 J at week one to 545719 ± 130374 J at week twelve ($p < 0.05$).

Interval Training

Each training week consisted of three days of interval training using 2 min work: 2 min active recovery bouts at 90% and 40% of $\dot{V}O_2$max, respectively, for a duration that allowed a total work output equivalent to what the subject would have performed if assigned to the continuous training group. Total work output was calculated as a combination of both the high intensity (i.e., 90% $\dot{V}O_2$max) and low intensity (i.e., 40% $\dot{V}O_2$max) phases of the workout. Participants were instructed to pedal at a constant cadence of 80 revs·min^{-1}. Work rates were modified throughout training according to the exercising heart rate range achieved during the first week of training (i.e., ±2.5%) to reflect changes in the participants' fitness. The average work output per session was similar to that of the continuous training group, increasing from 269052 ± 61613 J at week one to 516987 ± 80674 J at week twelve. Blood volume and the volume-regulating hormones were measured at weeks one, three, six, nine and 12 of training (as described later).

On weeks six and 12, participants participated in three days of interval training (as outlined above) and then repeated the testing done during the pre-test session.

Control

The participants that were randomly selected to the control group were to not engage in aerobic training and were encouraged to maintain their regular daily activities. They underwent the previously described measurements at baseline and at week 12.

Measurement Techniques

Incremental Exercise Tests

The exercise test protocol consisted of incremental to maximum exercise on an electronically braked cycle ergometer (107). The resistance on the ergometer was progressively increased to elicit staged steady-state conditions at predetermined target heart rates (± 5 beats) of 110, 130, 150 beats$\cdot$min^{-1} to maximum heart rate. Participants were instructed to maintain a pedalling cadence of 80 revs$\cdot$min^{-1} throughout the incremental test.

Oxygen Uptake

Oxygen uptake was measured using open circuit spirometry (101) according to the calculations provided in Appendix A. Expired gas and ventilatory parameters were assessed every 20 sec using a calibrated metabolic system (Quinton Metabolic Cart, California). The metabolic system was calibrated for oxygen and carbon dioxide concentrations and volume before and after each exercise test. The major criteria for the establishment of $\dot{V}O_2$max was the fulfillment of a plateau in $\dot{V}O_2$. Secondary criteria included: 1) volitional fatigue, 2) attainment of maximal heart rate, or 3) a respiratory exchange ratio greater than 1.10.

Ventilatory Thresholds

A two threshold model was utilized for the determination of aerobic (AerT) and anaerobic thresholds (AnT). Aerobic threshold was determined as the breakpoint in the relationship between $\dot{V}_E/\dot{V}O_2$ over time. Anaerobic threshold was determined as the breakpoint in the relationship between $\dot{V}_E/\dot{V}CO_2$ over time (64). Ventilatory thresholds were independently determined by two investigators. Inter-investigator variability was less than 5%.

Determination of Heart Rate and Blood Pressure During Incremental Exercise

During all testing sessions, heart rate was continuously monitored with a 12 lead electrocardiogram (ECG). Blood pressure (systolic (SBP) and diastolic (DBP)) was determined with a sphygmomanometer and a stethoscope placed on the participant's right arm, while seated on the cycle ergometer. Mean arterial pressure (MAP) was determined using the formula: DBP + ⅓ pulse pressure (SBP-DBP). Measurements were made during rest and at every predetermined stage of exercise during the incremental exercise tests (approximately every 4 min) and immediately upon the cessation of exercise.

Radionuclide Ventriculography During Incremental Exercise

Radionuclide ventriculography was conducted at rest and during incremental exercise on all test days (as previously described in Chapter Three). Participants exercised on a specially designed semi-recumbent cycle ergometer, which minimized the problems associated with movement artifact (as discussed in Chapter Three). This is essential for the accurate determination of LV volumes during exercise conditions (105). All radionuclide assessments were performed by a radionuclide technician who was blind to the treatment condition of the participant..

Myocardial Oxygen Consumption

Myocardial oxygen consumption ($M\dot{V}O_2$) was estimated using the product of heart rate and blood pressure (i.e., RPP ($mmHg \cdot min^{-1}$)) and calculated according to original methods of Suga and coworkers (100) as described by Kanstrup et al. (50) (refer to Chapter Three).

Haematologic Measurements

Blood Collection

Blood measurements were taken before training, at weeks one, three, six, nine and 12 in the continuous and interval training groups. The control group had resting blood measures taken at the start of the investigation and then 12 weeks later. All blood collection procedures were conducted by qualified personnel, certified in the collection and administration of fluid through intravenous means.

Upon reporting to the laboratory, the participants were required to lay supine for approximately 30 min. A rubber tourniquet was placed around the upper arm. The initial venous blood sampling was taken using a 19 ¾ gauge butterfly cathelon with 12" tubing (Vacutainer ® Blood Collection Set, Becton-Dickinson and Company, Franklin Lakes, N.J.) placed in an antecubital vein. Two three-way nylon stopcocks (MedexInc, Hillard, Ohio) were attached in series to the 12" tubing of the Vacutainer ® blood collection set. All components of the blood collection apparatus were chilled at 4°C prior to blood sampling. The butterfly hub of the cathelon was taped to the arm to prevent movement during sampling. Immediately upon entry of the cathelon into the blood vessel the rubber tourniquet was removed. All blood samples were collected into pre-chilled disposable plastic syringes (Becton-Dickinson and Company, Franklin Lakes, N.J.). An initial blood sample (3 to 5 mL) was taken using a 5 mL disposable plastic syringe (Becton-Dickinson and Company, Franklin Lakes, N.J.) attached to the first three-way stopcock. This blood sample was disposed of immediately after withdrawal. A second chilled 10 mL disposable plastic syringe was applied to the second three-way stopcock for the collection of 10 mL of whole blood. Of this sample, 7 mL were immediately transferred to chilled polypropylene tubes containing EDTA and aprotinin (0.6 $\mathrm{TIU \cdot mL^{-1}}$ of whole blood) for the measurement of α-atrial natriuretic peptide and angiotensin II. The remaining 3 mL were transferred to a 3 mL green-topped vacutainer (Vacutainer ®, Becton-Dickinson and Company, Franklin Lakes, N.J.) containing sodium heparin as anti-coagulant (for the measurement of aldosterone in heparinized plasma (not reported in this investigation). A final 10 mL sample was withdrawn from the blood collection apparatus into a chilled plastic syringe. Seven mL of this sample were transferred to a 7 mL green-topped vacutainer (Vacutainer ®, Becton-Dickinson and Company, Franklin Lakes, N.J.) containing sodium heparin as the anti-coagulant. This blood was used as the reference blood sample in the BV determination (as discussed later). The remaining 3 mL was transferred to a plain 12 X 75 mm disposable borosilicate glass culture tube

(FisherBrand®, Cat. No. 14-961-26, Fisher Scientific, Pittsburgh, P.A.). This blood was used for the assessment of haematocrit, haemoglobin and aldosterone (in serum) (as discussed later).

Following the blood sampling, the procedures for Evans blue determination of BV were commenced (as discussed later). Following the complete infusion of Evans blue dye, the cathelon was removed from the participant's arm. Ten minutes later, a second 19 ¾ gauge butterfly cathelon with 12 inch tubing (Vacutainer ® Blood Collection Set, Becton-Dickinson and Company, Franklin Lakes, N.J.) was placed in an antecubital vein of the contralateral arm and attached to a 7 mL green-topped vacutainer (Vacutainer®, Becton-Dickinson and Company, Franklin Lakes, N.J.). This blood was used as the "Dyed Plasma" sample in the BV calculations. After the removal of each cathelon the participant was instructed to hold firmly a sterile gauze pad (Johnson and Johnson Inc., Tor., Ont.) over the puncture point for several minutes, to minimize the likelihood of a haematoma developing. All blood (except that allowed to clot) was immediately put onto ice before processing. Once a blood clot had formed in the untreated whole blood (approximately 10 min), all blood samples were spun at 7,000 revs·min^{-1} at 4°C for 15 min (IEC CENTRA-7R, International Equipment Company, Needham Heights, MASS). The plasma for the measurement of hormones was transferred via cooled pipette tips to labelled 1.5 mL polypropylene microcentrifuge tubes (G-Tube™, Fisher Scientific, Nepean, Ont.). The samples were stored at -80°C (Cryo-Fridge, American Scientific Products, Golden, C.O.) until analysis.

Haematocrit

Blood for the determination of haematocrit was taken from the 3 mL untreated whole blood, immediately after withdrawal (before clotting had taken place). Haematocrit was determined in quadruplicate using pre-heparinized capillary tubes (FisherBrand®, Cat. No. 22-362-566, Fisher Scientific, Pittsburg, P.A.). The capillary tubes were sealed (Critoseal, Oxford Labware, St. Louis, M.O.) and placed inside a centrifuge (Micro-capillary Centrifuge, Model MB, International Equipment Company, Needham Heights, MASS). The tubes were spun at 7,000 revs·min^{-1} for 10 min. The percentage of the red blood cells in the total volume of the capillary tube (i.e., haematocrit) was determined using a microhaematocrit reader (Micro-capillary Reader Cat. No. 2201, International Equipment Company, Needham Heights, MASS.). The mean value of the four determinations was reported as the final haematocrit value (excluding outliers). The same experimenter performed all BV measurements to prevent inter-tester variability.

Haemoglobin Concentration

Haemoglobin concentration was measured in quadruplicate using the cyanmethomoglobin method as described in the Sigma technical bulletin (#525, Sigma Chemical Co., St. Louis, M.O.). Twenty μL of whole blood from the 3 mL untreated blood was delivered into 5 mL of prepared Drabkin's solution (Sigma Chemical Co., St. Louis, M.O.) into plain 12 X 75 mm disposable borosilicate glass culture tubes (FisherBrand®, Cat. No. 14-961-26, Fisher Scientific, Pittsburg, P.A.). The Drabkin's solution converts the haemoglobin into cyanmethomoglobin, which is a stable substance that has a maximum absorbency at 540 nm (Spectronic 601, Milton Roy Company, USA). The haemoglobin concentration of the sample was then determined by comparison to a standard curve of various dilutions of a known standard containing a haemoglobin concentration of 20 $g \cdot dL^{-1}$. The same experimenter performed all BV measurements to prevent inter-tester variability.

Evans Blue Dye Assessment of Blood Volume

Blood volume was determined using Evan's blue dye (T-1824, New World Trading Corporation, DeBary, FL) in a standard dilution technique. Participants were instructed to refrain from drinking alcoholic beverages and exercising for at least 12 hours prior to the BV measurement. Participants came into the laboratory at approximately the same time of the day for each assessment of BV and all other blood measures. Upon arrival, the participant was required to lay in a supine position for a period of 30 min. During this time, 3 to 4 mL, depending on the participant's mass, of dye was weighed on a high precision scale to determine exact volume (see Appendix B). A 10 mL reference sample was withdrawn (as described above) for the reference sample. The dye was slowly injected into the antecubital vein. Once the injection was completed the cathelon was flushed two times with 10 mL of saline solution (0.9% sodium chloride) to ensure that all traces of dye were infused. After a period of 10 min a second 10 mL syringe was withdrawn from the contralateral arm (as discussed previously). All blood samples were then centrifuged at 7,000 revs·min^{-1} at 4°C for 15 min. The absorbency of the plasma of each sample was measured at 610 nm in a spectrophotometer. Total plasma volume (PV) and BV were determined using standard formulas as outlined in Appendix D (6). The same experimenter performed all BV measurements to prevent inter-tester variability.

Radionuclide Assessment of Blood Volume

To further assess BV, a 5 mL sample of blood was withdrawn 10 min after the radionuclide tracer administration (during the testing session before exercise) from an antecubital vein. Determination of the level of radioactivity in the 5 mL sample and assessment of the total radioactive dose administered (correcting for the amount initially in the syringe and the amount remaining after administration) allowed for the measurement of total BV by the dilution principle (3, 81) (as described in Chapter Three). The same experimenter performed all BV measurements to prevent inter-tester variability.

Radioimmunoassay Methods

The radioimmunoassay (RIA) methods were based on standard laboratory procedures using RIA kits supplied by Phoenix Pharmaceuticals, California. In brief, the assay was based on the competition of a radiolabelled ^{125}-I-peptide and the unknown (or standard) peptide for limited amounts of antibodies that are specific for the peptide. With increasing amounts of the peptide the ability of the ^{125}-I-peptide to bind to the antibody was reduced. Creation of a "standard curve" using known concentrations of the standard peptide in combination with the ^{125}-I-peptide allowed for the calculation of the concentration of the peptide of interest in the unknown samples.

For the measurement of α-atrial natriuretic peptide and angiotensin II measurements 10 mL of whole blood was transferred into chilled polypropylene tubes containing EDTA and aprotinin (0.6 TIU·mL^{-1} of whole blood). The tubes were gently oscillated several times to prevent coagulation (via EDTA) and inhibit the activity of proteinases (via aprotinin). All blood samples were centrifuged at 7,000 revs·min^{-1} for 15 min at 4°C, and the plasma was stored at -80°C until analysis.

Before the assay, the plasma samples were allowed to come to room temperature and gently inverted. The α-atrial natriuretic peptide and angiotensin II were measured according to the procedures of the manufacturer of the RIA kit (Phoenix Pharmaceuticals, California) as outlined in Appendix C. In brief, α-atrial natriuretic peptide and angiotensin II were extracted from the plasma using buffers consisting of 1% trifluoroacecetic acid (TFA, HPLC Grade) in water and 60% acetonitrile (HPLC Grade) in 1% TFA, centrifuged and eluted using a C_{18} Sep-Pak extraction column (RK-SEPCOL-1, Phoenix Pharmaceuticals, California). The eluent was dried by evaporation using a lyophilizer. The residue was dissolved in 250 μL of RIA buffer and duplicate aliquots of each sample (100 μL per tube) were incubated with the primary antibody (rabbit anti-peptide serum) for 24 hours at 4°C. This was followed by the addition of ^{125}I-labelled-peptide (^{125}I-α-atrial natriuretic peptide or ^{125}I-angiotensin II) and a second 24 hour incubation at 4°C. A secondary antibody (i.e., goat anti-rabbit IgG serum) and normal rabbit serum were then added to the samples and a third incubation for 90 min at room temperature was conducted. Following the third incubation, 500 μL of RIA buffer was added to each tube, which was followed by another centrifugation at 3,000 revs·min^{-1} for 20 min at 4°C to separate bound and unbound α-atrial natriuretic peptide or angiotensin II. The supernatant was carefully aspirated off and the radioactivity of the remaining pellet was assessed using a gamma camera. The extraction efficiency of known amounts of α-atrial natriuretic peptide or angiotensin II was estimated at 80%. All samples were assayed in duplicate in the same assay. The inter-assay coefficient of variation for duplicate measures was 5.5% for α-atrial natriuretic peptide and 3.4% for angiotensin II.

For the measurement of aldosterone, 5 mL of whole blood was collected into plain 12 x 75 mm tubes. A clot was allowed to develop followed by centrifugation at 7,000 revs·min^{-1} for 15 min at 4°C. The serum was stored at -80°C until analyses. The assay was performed on unextracted serum according to the Coat-A-Count procedures

(Diagnostic Products Corporation, Canadian supplier Intermedico, Markham) as outlined in Appendix F. All samples were assayed in the same assay. The inter-assay coefficient of variation for duplicate measures of aldosterone was 2.5%. According to the manufacturer's Coat-A-Count instructions (Diagnostic Products Corporation, Canadian supplier Intermedico, Markham) maximal binding is 40% and the detection limit is 16 $pg \cdot mL^{-1}$. The cut-off coefficient of variation for duplicate measures of the hormones of interest was >15%.

Resting Echocardiographic Measurements

Resting echocardiographic measurements were taken on the three test days (i.e., baseline, week six and week 12). The left ventricle was imaged with a Hewlett-Packard ultrasound instrument (Sonos 5500, Hewlett-Packard, Massachussetts) with a 3.5 MHz transducer and recorded in the left lateral decubitus position during quiet respiration. Left ventricular morphology was examined using the parasternal short axis view. M-mode measurements of right ventricular dimension in diastole (RVIDd) and systole (RVIDs), left ventricular internal dimension in diastole (LVIDd) and systole (LVIDs), ventricular septal wall thickness in diastole (VSTd) and systole (VSTs), and posterior wall thickness in diastole (PWTd) and systole (PWTs) were examined in accordance with the American Society of Echocardiography guidelines (87) by a echocardiographer who was blind to the treatment condition of the participant. Left ventricular mass was estimated according to the corrected American Society of Echocardiography formula (17) as follows:

$$\text{Left ventricular mass (g)} = 0.8\,[(\text{PWTd} + \text{LVIDd} + \text{VSTd})^3 - \text{LVIDd}^3] + 0.6.$$

Meridional wall stress during systole (an index of myocardial afterload) was calculated using the formula of Grossman et al. (43) as previously reported by our laboratory (45):

$$\text{Wall Stress (mmHg)} = (0.334 \times \text{SBP} \times \text{LVIDs})/[\text{PWTs} \times (1 + \text{PWTs}/\text{LVIDs})]$$

Doppler Echocardiography

Doppler echocardiography was utilized to assess resting measures of cardiac function. For the pulsed wave Doppler measurement of diastolic transmitral flow velocities a 2.5 MHz transducer was placed at the suprasternal notch to obtain an apical four chamber view of the myocardium, with the sample volume located at the tips of the mitral valve leaflets towards the interior of the left ventricle. Left ventricular flow velocity waveforms from three resting cardiac cycles were averaged for the measurement of the following diastolic parameters: a) early peak filling velocity (E), b) peak atrial filling velocity (A), and c) the E/A ratio.

The velocity of blood in the ascending aorta was evaluated using the Doppler transducer. The velocity time curve over time was traced off-line, with computer integration of the velocity time integral (VTI). The diameter of the aorta was measured with M-mode echocardiography at the level of the aortic annulus with the assumption that the aorta was circular. Aortic cross-sectional area (ACSA) was measured according to the formula: ACSA (cm^2) = $\pi d^2/4$, where d equals the aortic diameter. Resting SV was calculated as the VTI ·ACSA. Left ventricular ejection time was calculated as VTI/mean velocity. Diastolic filling time was calculated as the period of time from the closure of the aortic valve to the onset of ventricular excitation of the next heart beat. M-mode and Doppler echocardiographic measurements were immediately analyzed by an experienced echocardiographer.

Anthropometric Measurements

Body mass was measured with the participant wearing a light t-shirt and shorts using a calibrated scale (Healthometer, Continental Scale Corporation, Bridgeview, Illinois, U.S.A.). Measures of body mass were taken before and after each test to the nearest ± 0.2 kg.

STATISTICS

Descriptive and inferential statistical analyses of all data were conducted using STATISTICA™. The acceptable level of significance was set *a priori* at $p \leq 0.05$. All measurements subjected to inferential analyses were reported as mean and standard deviation of the mean (SD). The cardiorespiratory and blood measurements were analyzed using appropriate analysis of variance (ANOVA). Tukey *post hoc* comparisons were used to identify differences between means when main effects were observed. Simple linear regression was utilized to establish the relationship(s) between the cardiovascular parameters of interest.

RESULTS

The baseline characteristics of the participants are shown in Table 4.1. All participants were normally active individuals with as reflected by their low mean $\dot{V}O_2$max of 39.1 ± 7.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ and their low relative mean BV of 64.2 ± 9.3 $mL{\cdot}kg^{-1}$. It is important to note, that their $\dot{V}O_2$max is somewhat lower than that normally reported for sedentary individuals. This is likely the result of exercise in the semi-recumbent position, since we have previously shown that participants can achieve a higher $\dot{V}O_2$max during upright exercise versus supine exercise (as discussed in Chapter Three). As such, the $\dot{V}O_2$max values may actually represent a peak $\dot{V}O_2$ rather than a true $\dot{V}O_2$max. Analysis of variance of all measures of interest at pre-test revealed no significant difference between the continuous training, interval training and control groups (including all participants) with regards to any measure. This highlights the success of the randomization procedures. This statistical equivalency remained even after the dropout data was removed from the analysis, thereby indicating that the dropouts occurred in a random fashion.

Control Group

No significant changes occurred in the dependent measures of interest in the control group over the 12-week period. Continuous and interval training resulted in a series of significant changes as outline below.

The Effects of Training on Vascular Volumes

In absolute terms, there was no significant change in BV, PV or red cell volume (RCV) within the continuous and interval training groups, despite a relatively large increase in both groups. This is likely owing to the small sample size (i.e., low statistical power) and large variability in this measure (especially in the continuous group). A large portion of the variability in the measure of vascular volumes appeared to be due to the variance in body mass within the continuous group. Analysis of the data accounting for differences in body mass removed a large portion of the variability in the measures of vascular volume (Table 4.2). Similar to the findings with regards to absolute changes in vascular volume, there were no significant changes in vascular volume when expressed relative to body mass (Table 4.2). However, percent changes were large, further supporting the impact a small sample size has on these findings.

Percent Changes in Absolute Blood Volume

The control group did not experience a significant change in vascular volumes over the 12 wk period (Table 4.2). As illustrated in Figure 4.1, there were significant changes in BV, PV, and RCV as a result of training. The increase in BV during the early stages of training was due largely to an elevation in PV. Increases in RCV were more gradual, reaching statistical significance after week three of training.

The percent increases in BV, PV, and RCV across the twelve weeks of training were slightly larger after the continuous training in comparison to the interval training (Table 4.2, Figure 4.1). Analysis of variance of the mean changes in vascular volumes across all training weeks revealed that there were significantly greater percent changes in BV and PV in the continuous training group versus the interval training group. The mean BV expansion across all weeks for the continuous training group was 11.2 ± 7.2% versus 7.9 ± 5.3% for the interval training group ($p < 0.05$). The mean PV expansion was 11.4 ± 7.1% for the continuous training group versus 7.1 ± 6.9% for the interval training group ($p < 0.05$). Percent changes in RCV were also slightly higher in the continuous training group versus the interval training group (10.9 ±10.5 versus 9.4 ±7.4, respectively). However, these results did not achieve statistical significance.

Percent Changes in Relative Vascular Volumes

The percent changes in vascular volumes expressed relative to body mass were similar to the percent changes in absolute vascular volumes (Table 4.2). The control group experienced no significant changes in percent changes in vascular volume expressed relative to body mass. Both continuous training and interval training resulted in a significant improvement in percent increases in relative vascular volumes over the 12-week period.

The mean percent increases in relative BV and PV across the 12 weeks of training were significantly larger in the continuous training group versus the interval training group (11.7 ± 7.0 versus 8.0 ± 5.7%, 12.0 ± 7.0 versus 7.1 ± 7.4%, respectively, p <

0.05). The percent changes in relative RCV were also slightly, but not significantly greater in the continuous training group in comparison to the interval training group (10.9 ± 10.5 versus 9.4 ± 7.4%, respectively).

Cardiorespiratory Measures

The changes in pre-exercise and maximal cardiorespiratory measures as a result of training are shown in Tables 4.3 and 4.4. No significant differences were seen in pre-exercise measures of HR, $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$), SBP (mmHg), DBP (mmHg), MAP (mmHg), $\dot{V}_E$ ($L \cdot min^{-1}$), and oxygen pulse (i.e., the ratio of $\dot{V}O_2$ to HR) ($mL \cdot beat^{-1}$) after training. However, there were significant changes in several cardiorespiratory measures during maximal exercise including $\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$), $\dot{V}_E$ ($L \cdot min^{-1}$), and oxygen pulse. For clarity, each of these parameters will be discussed separately.

Heart Rate

Heart rate increased throughout incremental exercise, reaching its maximum value during maximum exercise. Endurance training had no significant effect on resting heart rate (as evaluated in the semi-recumbent position before the exercise test) or the heart rate response to incremental to maximum exercise (Tables 4.3 and 4.4).

Blood Pressure

Systolic Blood Pressure

There were no significant changes in SBP at rest or during incremental exercise (Tables 4.3 and 4.4) over the 12-week period. During exercise, there was an incremental increase in SBP, with the highest value being observed during maximal exercise ($p < 0.05$) (Figure 4.2).

Diastolic Blood Pressure

The were no significant changes in resting or exercise DBP after 12 weeks of training. Diastolic blood pressure was also similar at rest and during each stage of exercise irrespective of treatment condition (Tables 4.3 and 4.4) (Figure 4.3).

Mean Arterial Blood Pressure

Mean arterial blood pressure was not significantly affected by endurance training (Tables 4.3 and 4.4). Mean arterial blood pressure generally increased during incremental exercise. The MAP observed at 150 beats·min^{-1} was not significantly different from that at 130 beats·min^{-1} and at maximum heart rate. Otherwise, the MAPs at all other staged heart rates were significantly different from each other (Figure 4.4).

Oxygen Consumption

Oxygen consumption in each group increased in a linear fashion throughout incremental to maximum exercise during each test condition ($p < 0.05$). There was no significant change in $\dot{V}O_2$ at rest or throughout incremental exercise in the control group over the twelve weeks of the investigation (Tables 4.3 and 4.4). Both the continuous and interval training groups resulted in a significant increase in the $\dot{V}O_2$ response to exercise after both week 6 and week 12 of training (Figure 4.5). There was no significant difference between the training groups between the $\dot{V}O_2$ response to incremental exercise. The rise in oxygen consumption was predominantly due to an increase in $\dot{Q}$, since training had little effect on arterio-venous oxygen difference (a-$\bar{v}DO_2$) (as discussed later).

Maximal Aerobic Power

Maximal aerobic power was not significantly increased over the twelve weeks in the control group (Table 4.4). Whereas, both the continuous and interval training groups achieved significant improvements in $\dot{V}O_2$max (Figure 4.6). Again there was no significant difference between the continuous and interval training groups. However, the mean percent increase in $\dot{V}O_2$max after 6 weeks and 12 weeks of training was slightly larger in the continuous training group versus the interval training group (Figure 4.6). The overall mean increase in $\dot{V}O_2$max across all 12 weeks was 21.4 ± 12.8% versus 16.7 ± 10.9% in the continuous and interval training groups, respectively.

Minute Ventilation

Minute ventilation increased in a linear fashion throughout incremental to maximum exercise during each test condition irrespective of the treatment group ($p < 0.05$) (Figure 4.7). There was no significant change in the $\dot{V}_E$ (L·min^{-1}) response to exercise in the control group over the 12-week period (Table 4.4). Analysis of the effects of training at weeks six and 12, revealed that ventilation was significantly higher at both weeks 6 and 12. No significant difference existed in $\dot{V}_E$ between the interval and continuous training groups (Table 4.4).

Oxygen Pulse

Oxygen pulse increased throughout incremental to maximum exercise during each test period in all groups ($p < 0.05$) (Figure 4.8). No significant change in oxygen pulse occurred in the control group over the 12-week period (Tables 4.3 and 4.4). Analysis of the effects of training on oxygen pulse revealed that oxygen pulse was significantly increased after 6 weeks of training in both training groups (Table 4.4). Oxygen pulse was slightly, but not significantly increased after 12 weeks of training ($p = 0.09$). No significant difference existed between the continuous and interval training groups (Tables 4.3 and 4.4).

Effects of Aerobic Training on Ventilatory Thresholds

There were no significant changes in ventilatory thresholds (in absolute or percentage terms) in the control group over the 12-week period. Oxygen consumption at AerT and AnT increased by a similar amount in both the continuous and interval training groups (Table 4.5). The increases in AerT after training were only significant after 12 weeks of training. Whereas, the increase in AnT after training was significant after both weeks six and 12. Relative ventilatory thresholds (expressed as percentages of $\dot{V}O_2$max) were unchanged following training in both the continuous and interval training groups (Table 4.5).

Power Output

Peak power output did not significantly change over the 12-week period in the control group. Interval and continuous training resulted in similar increases in peak power output after both weeks 6 and 12 (Table 4.5).

Resting Myocardial Function

As shown in Table 4.6, there was no significant change in several indices of resting (pre-exercise) myocardial function (as evaluated by radionuclide ventriculography) including EF, $\dot{Q}$, SV, EDV, ESV, time to peak ejection (TPE), time to peak filling (TPF), peak ejection rate (PER), peak filling rate (PFR), and SBP/ESV.

Exercise Myocardial Function

No significant change in exercise cardiac function was also seen after training with regards to EF, TPF or SBP/ESV. In contrast, training resulted in significant changes in $\dot{Q}$, SV, EDV, ESV, TPE, PER, and PFR (Table 4.7). Each of these parameters will be discussed separately.

Ejection Fraction

Ejection fraction was significantly increased throughout exercise in comparison to rest (Figure 4.9). There was no significant change in resting or exercise EF as a result of endurance training. Ejection fraction in the control group also remained at a similar level over the 12-week period.

Cardiac Output

During the initial baseline test, $\dot{Q}$ increased up to 150 beats·min^{-1} and then levelled off. After both continuous and interval training $\dot{Q}$ increased in a linear fashion throughout incremental exercise (Figure 4.10). There was no significant difference in the $\dot{Q}$ response to exercise in the control group over the 12-week period. Analysis of the effects of aerobic training on the $\dot{Q}$ response to exercise revealed that $\dot{Q}$ was significantly increased after both weeks 6 and 12 throughout incremental to maximal exercise. There was no significant difference between the continuous and interval training groups, despite the continuous training group exhibiting a slightly larger $\dot{Q}$ at each stage of exercise than the interval training group. The increase in $\dot{Q}$ after both continuous and interval training was largely due to an increase in SV, since training resulted in minor changes in heart rate.

Stroke Volume

The SV response to exercise was somewhat different before and after training (Figure 4.11). Before training, SV reached its maximum value at a heart rate of 110 to 130 beats·min^{-1} and then declined (Figure 4.11). After both interval and continuous training, SV continued to increase throughout incremental exercise, reaching its maximal value during maximal exercise (Figure 4.11). However, similar to the findings reported in Chapter Three, there was no significant difference between the SV at 110 beats·min^{-1} and that observed at the stages heart rates of 130 and 150 beats·min^{-1} and maximal heart rate.

Analysis of the effects of aerobic training on SV revealed that SV was increased after both weeks 6 and 12. No significant difference in SV existed between the continuous and interval training groups. The SV response to exercise of the control group did not significantly change over the 12-week period.

End-diastolic Volume

Across all conditions, EDV at rest was significantly lower than that the EDV observed at each staged heart rate (Figure 4.12). The EDV at all other exercise heart rates were not significantly different from one another. The EDV response to exercise was somewhat different after training. Before training, EDV reached its maximum value at approximately 110 to 130 beats·min^{-1} and thereafter declined to near baseline values (Figure 4.12). After both continuous and interval training, EDV increased gradually throughout incremental exercise, allowing SV to also increase (as previously discussed).

No significant changes in EDV occurred in the control group over the 12-week period. There was a main effect for time of training with significant improvements in EDV beginning at six weeks of training (Figure 4.12). The EDV at week 12 of training was also larger than that observed before training, however, this difference did not achieve statistical significance ($p = 0.07$). There was no significant difference between the EDV response to exercise of the continuous and interval training groups.

End-systolic Volume

End-systolic volume decreased in a progressive fashion during incremental exercise, reaching its lowest value during maximal exercise (irrespective of condition) (Figure 4.13). Training had no significant effect on the ESV response to incremental exercise (Figure 4.13).

Time to Peak Ejection

Time to peak ejection decreased in a linear fashion throughout incremental exercise (Figure 4.14). There was no significant change in the control group over the 12-week period. Analysis of the training data revealed that there was a significant main effect for time of training. The TPE observed at week six was slightly, but not significalntly, less than that achieved during baseline testing ($p = 0.14$). The TPE observed after 12 weeks of training was significantly less than that observed before training ($p = 0.047$). There was no significant difference between the TPE response to exercise between the continuous and interval training groups (Figure 4.14).

Time to Peak Filling

Time to peak filling decreased throughout exercise irrespective of the treatment condition or experimental group (Figure 4.15). Training had no significant impact on TPF.

Peak Ejection Rate

Peak ejection rate increased in a linear fashion throughout incremental exercise ($p < 0.05$) (Figure 4.16). There was no significant change in the PER response to exercise in the control group over the 12-week period. Endurance training resulted in a significant improvement in the PER response to incremental exercise after both week 6 and week 12 of training ($p < 0.05$). The continuous training group also had a significantly greater PER in comparison to the interval training group ($p < 0.05$) (Figure 4.16). However, the magnitude of changes in PER were similar between groups.

Peak Filling Rate

Peak filling rate increased throughout incremental exercise irrespective of treatment condition or experimental group ($p < 0.05$) (Figure 4.17). Training resulted in a significant improvement in PFR after both weeks six and 12 of training ($p < 0.05$). The changes in PFR rate were similar between the continuous and interval training groups (Figure 4.17).

Systolic Blood Pressure to End-systolic Volume Ratio

The SBP/ESV increased during incremental exercise (Figure 4.18). The SBP/ESV response to exercise did not significantly change in the control group over the 12-week period. The continuous and interval training groups did not differ with respect to the SBP/ESV response to exercise. There was a slight reduction in the SBP/ESV response to exercise after 6 weeks of training ($p < 0.05$), but this difference was removed after 12 weeks of training.

Arterio-venous Oxygen Difference

Arterio-venous oxygen difference increased in a linear fashion throughout incremental exercise (Figure 4.19). Arterio-venous oxygen difference did not significantly change in the control group or after either endurance training program (Figure 4.19).

Myocardial Oxygen Consumption and its Determinants

Stroke Work

There was no significant change in calculated SW during incremental exercise in the control group over the 12-week period. Training resulted in a significant improvement in the SW response to exercise after six weeks of training ($p < 0.05$), and a slight but non-significant improvement after 12 weeks of training ($p = 0.12$) (Figure 4.20). No significant difference existed between the continuous and interval training groups.

Potential Energy

There was no significant difference in calculated PE between staged heart rates, irrespective of treatment condition. There was no significant change in PE over the 12-week period in the control group. Six weeks of training resulted in a significant increase in PE in comparison to baseline and week 12 of training ($p < 0.03$) (Figure 4.21). The training groups were not significantly different from each other.

Pressure Volume Area

The calculated PVA response to incremental exercise was unchanged in the control group over the 12-week period (Figure 4.22). Training resulted in a significant improvement in the PVA response to exercise after 6 weeks ($p < 0.05$), and a slight improvement after 12 weeks ($p = 0.08$). There were no significant differences in the PVA response to exercise between the continuous training and the interval training groups.

Myocardial Oxygen Consumption

The calculated $M\dot{V}O_2$ increased in a linear fashion throughout incremental exercise ($p < 0.05$) (Figure 4.23). There was no significant change in calculated $M\dot{V}O_2$ in the control group over the 12 weeks of the investigation. Endurance training resulted in a significant increase in calculated $M\dot{V}O_2$ after six weeks of training ($p < 0.05$), and a slight increase in calculated $M\dot{V}O_2$ after 12 weeks of training ($p = 0.13$). There was no significant difference between the continuous and interval training groups (Figure 4.23).

Rate-pressure Product

Rate-pressure product increased in a linear fashion throughout incremental to maximum exercise ($p < 0.05$) (Figure 4.24). There was no significant change in the RPP response to exercise in the control, interval training or the continuous training groups over the period of the investigation.

Net Myocardial Efficiency

Net myocardial efficiency at rest was significantly less than that at each stage of exercise ($p < 0.05$) (Figure 4.25). Training had no significant impact on net myocardial efficiency (Figure 4.25).

Echocardiographic Measurements of Left Ventricular Morphology and Function

Table 4.8 contains a summary of the changes in resting LV morphology over the 12 weeks of the investigation. As shown in Table 4.8, no significant change occurred in the M-mode measurements of RVIDd, RVIDs, LVIDd, LVIDs, VSTd, VSTs, PWTd, and PWTs. There was also no significant change calculated LVM or resting aortic diameter. Resting fractional shortening (FS) also did not significantly change after training. This is quite similar to the radionuclide ventriculography findings for EF (which is a surrogate for FS). This provides further support to the finding that resting LV performance is relatively unchanged after short term training. Resting meridional wall stress was also not significantly altered by short term training (Table 4.8)

Doppler Assessment of Resting Left Ventricular Function

As shown in Table 4.9, resting measures of diastolic or systolic function as determined by Doppler echocardiography were generally not significantly affected by training. Only resting diastolic filling time increased after 6 weeks of endurance training, but this difference did not remain after 12 weeks of training (Table 4.9). Resting measures of diastolic function including E velocity, A velocity, and E/A ratio did not significantly change over the 12-week period irrespective of the treatment condition. Similarly, the systolic indices of VTI, SV, and LV ejection time were not significantly affected by endurance training. Again this finding is quite similar to that observed with radionuclide ventriculography.

Resting Volume-Regulatory Hormones

No significant changes in resting concentrations of aldosterone, or α-atrial natriuretic peptide occurred during this investigation despite concomitant increases in vascular volumes (Figures 4.26 to 4.27, Table 4.10). However, the resting concentration of angiotensin II increased significantly after week one of continuous and interval training and then afterwards declined to levels that were somewhat below the baseline values (Figure 4.28). To evaluate whether the total amount of each hormone was increased after training, each hormone concentration was expressed relative to the changes in PV (Figures 4.26 to 4.28). No significant changes in the total amount of aldosterone, or α-atrial natriuretic peptide occurred during the 12-weeks of the investigation. There was however a slight trend for the total amount of aldosterone to increase throughout training as illustrated in Figure 4.26. The total amount of angiotensin II followed a similar pattern to the resting plasma concentration of angiotensin II, reaching its highest value at week one and then declining from weeks three to 12 (Figure 4.28).

Correlations

Simple correlation analyses were conducted to evaluate the relationship between changes in vascular volumes and changes in $\dot{V}O_2$max (in both relative and absolute terms) in the endurance training groups (Table 4.11) (Figure 4.29). Blood volume, PV, and RCV (expressed relative to body mass) were directly associated with both relative and absolute $\dot{V}O_2$max throughout training (Table 4.11). Changes in vascular volume accounted for a significant portion of the variance in the change in relative and absolute $\dot{V}O_2$max. For instance, percent changes in BV accounted for 56 and 54% of the variance in the percent changes in $\dot{V}O_2$max (in relative and absolute terms, respectively). Percent changes in PV accounted for 44 and 40% of the variance in the percent changes in $\dot{V}O_2$max (in relative and absolute terms, respectively). Percent change in RCV also accounted for a large portion of the variance in percent changes in $\dot{V}O_2$max in relative and absolute terms (44 and 45%, respectively). Figures 4.29 and 4.30 illustrated the various relationships between vascular volumes and relative $\dot{V}O_2max$ during training.

DISCUSSION

The primary objective of this investigation was to evaluate the impact of continuous and interval endurance training on BV, hormones involved in the regulation of BV, and LV morphology and function. The major findings of this investigation are that: a) both continuous training and interval training result in significant increases in vascular volumes, $\dot{V}O_2max$, and LV function during incremental exercise, b) the mean increases in BV and PV across all twelve weeks were significantly larger after continuous training in comparison to interval training, c) the changes in $\dot{V}O_2max$, and LV function were also slightly, but not significantly, larger after continuous training in comparison to interval training, d) the elevation in vascular volumes accounts for a large portion of the changes in $\dot{V}O_2max$.

Blood Volume Adaptations to Continuous and Interval Endurance Training

As discussed previously (Chapter Two), the average BV expansion resulting from short-term endurance training in men and women approximates 6% (ranging from 2 to 12%) (4, 13, 14, 25, 38-41, 56, 65, 66, 79, 80, 83, 94). The majority of these investigations examined the effects of continuous aerobic training on vascular volumes. A few investigators have also examined the impact of high intensity intermittent training on vascular volumes (40, 80). To the best of our knowledge, the present investigation is the first randomized controlled investigation to compare the adaptations in vascular volumes resulting from continuous and interval training. The present findings reveal that continuous training results in a significantly greater expansion of BV and PV in comparison to interval training (11.7 ± 7.0 versus 8.0 ± 5.7%, 12.0 ± 7.0 versus 7.1 ± 7.4%, respectively, $p < 0.05$). Similarly, the percent increases in RCV were slightly higher after continuous training in comparison to interval training (10.9 ± 10.5 versus 9.4 ± 7.4%, respectively).

Time Course of Adaptations in Vascular Volumes

In the present investigation, the BV expansion during the early stages of training was mainly the result of changes in PV. The increases in RCV were more gradual and did not achieve statistical significant until three weeks of training. Blood volume expansion peaked at week one and then remained at relatively the same level for the remainder of the training period in both the continuous and interval training groups. The early increase in BV as a result of PV expansion and the slower rise in RCV is similar to the findings of other investigators (1, 9-13, 38, 39, 41, 42, 80).

Others however have reported no significant change in vascular volumes after short-term training (94, 98). These discrepancies are likely related to differences in experimental protocols, training programs, environmental conditions and/or the seasons in which the research was conducted (94).

Vascular Volumes and Maximal Aerobic Power

A great deal of controversy exists regarding the impact of changes in BV on $\dot{V}O_2$max (47, 104, 106). Several investigators have discussed the importance of total haemoglobin on the determination of $\dot{V}O_2$max (32, 48, 49). However, recent investigators have revealed that $\dot{V}O_2$max may be increased via augmentation of BV, independent of changes in red blood cells (i.e., hypervolemic anaemia) in untrained individuals (as reviewed by Warburton et al. (104)). Thus, changes in BV may account for a larger portion of the enhancement in $\dot{V}O_2$max seen after short-term training than was once previously thought. In fact, previous investigators have postulated that a large portion of the improvement in cardiovascular function of endurance-trained athletes is directly related to their elevated BV (33-35, 52, 104, 107). The findings from the present investigation provide direct support for this hypothesis.

As reviewed by Warburton et al. (104) analysis of the relationship between BV and $\dot{V}O_2$max from reported values in the literature indicated that there is a direct relationship between BV and $\dot{V}O_2$max. According to Warburton et al. (104) BV accounts for approximately 56% of the variance in $\dot{V}O_2$max in men. In the present investigation, BV ($mL \cdot kg^{-1}$) also explained 56% of the variance in $\dot{V}O_2$max. Perhaps more importantly, the percent changes in $\dot{V}O_2$max resulting from training were directly associated with training-induced increases in vascular volumes. For instance, percent changes in BV accounted for 54% of the variance of changes in $\dot{V}O_2$max. Percent changes in PV and

RCV also accounted for a significant portion of the variance in percent changes in $\dot{V}O_2max$ after training. Therefore, it would seem that vascular volumes account for a significant portion of the variance in $\dot{V}O_2max$ in healthy men. Also, changes in vascular volumes after training are directly associated with changes in $\dot{V}O_2max$. This is supported by several investigations which observed a direct relationship between BV and $\dot{V}O_2max$ (9, 33, 52, 59, 66, 72, 99, 107, 108) and is contrary to investigations where no relationship between $\dot{V}O_2max$ and vascular volumes was found (89, 94, 109).

Effects of Continuous Versus Interval Training on Maximal Aerobic Power

There is considerable debate as to which training program (continuous versus interval training) will have a greater effect on $\dot{V}O_2max$ (15, 19, 36, 58, 71, 78). Some investigators have revealed that continuous training results in a greater improvement in $\dot{V}O_2max$ in comparison to interval training (88). Others have reported that interval training results in greater improvements in $\dot{V}O_2max$ (36), whereas others have observed no difference between the two methods with regards to $\dot{V}O_2max$ (15, 19, 78). A great deal of these discrepancies are related to failure to equate the initial fitness levels of groups, failure to equate total work output between groups, and failure to monitor and change training work rates according to improvements in fitness levels. In the present investigation we controlled for most of these potential confounding variables by matching and stratifying our participants according to body mass and initial fitness levels. Also, we equated the total work output between groups throughout training and adjusted the work rates according to improvements in fitness. As such, we feel confident that we were able to accurately evaluate the differential effects of continuous versus interval training on $\dot{V}O_2max$.

The findings from the present investigation indicate that continuous training and interval training result in similar improvements in $\dot{V}O_2max$. However, the continuous training groups did experience an increase in $\dot{V}O_2max$, which was slightly greater than that observed after interval training (approximately 5%).

Several authors have postulated that continuous and interval training would attain improvements in $\dot{V}O_2max$ through different mechanisms. For instance, it has been postulated that continuous training would stimulate central adaptations including an increased SV and $\dot{Q}$. This is due to the fact that continuous training requires the participant to train for prolonged periods of time at a submaximal SV and $\dot{Q}$. As such, the potential central adaptations resulting from continuous training are large (58). It also holds that the athlete will use predominantly aerobic metabolism, with little energy being supplied by anaerobic glycolysis and/or the adenosine triphosphate (ATP)-creatine phosphate (CP) system (36, 58). Likewise, continuous training will involve the predominant usage of slow-twitch fibres. Thus, the oxidative capacity of type I (slow-twitch) fibres are likely to be enhanced by continuous training (78).

Whereas, interval training (that utilizes work phases that approach or exceeds $\dot{V}O_2max$) is commonly believed to have minor central adaptations, and greater changes in the peripheral extraction (15, 58). For instance, MacDougall and Sale (58) postulated that tissue hypoxia provides the key stimulus for an increase in peripheral oxygen extraction. It has also been postulated that the greater the training intensity the greater the potential for peripheral adaptations (15). As such, interval training may provide the greatest adaptations in the peripheral extraction of oxygen. Interval training is thought to lead to an increased reliance on energy supplied from anaerobic glycolysis and the ATP-PC system. Also, as the exercise intensity increases the recruitment of type II fibres will increase. Therefore, interval training may result on an increased oxidative capacity of the type II fibres, and an increased capacity for anaerobic metabolism (36, 78).

In the present investigation, the change in $\dot{V}O_2max$ after both interval and continuous training were strongly related to increased SV and $\dot{Q}$, since minimal changes in the peripheral extraction of oxygen occurred over the training period. The major difference between the two groups with regards to $\dot{V}O_2max$ was related to differences in $\dot{Q}$. For instance, the $\dot{Q}$ response to exercise of the continuous training group was consistently higher than that observed in the interval training group. This was largely the result of an increased EDV leading to an increased SV (as discussed below). Therefore, in the present investigation, both interval and continuous training resulted in significant improvements in cardiac function with minimal changes in the peripheral extraction of oxygen. Continuous training resulted in slightly greater cardiac response, which allowed for a moderate improvement in $\dot{V}O_2$max in comparison to that seen with interval training. However, it is important to stress that these differences were minimal. If an improvement in $\dot{V}O_2$max is desired, but elevations in BV are not, interval training may be the preferred method of aerobic training.

Effects of Continuous versus Interval Training on Left Ventricular Function

Left Ventricular Systolic Function

Common indices of LV systolic function include EF (using radionuclide ventriculography), FS (using echocardiography), and the SBP/ESV ratio (using radionuclide ventriculography) (21). The present investigation had the unique opportunity to evaluate each of these parameters before and after continuous or interval training. No significant change occurred in these systolic parameters at rest after either continuous or interval training. This finding is supported by other investigators (21, 22, 44, 61, 92) and indicates that endurance training generally does not significantly alter the resting systolic parameters of EF, FS, and/or the SBP/ESV ratio. This is a similar finding to that of Pluim et al. (77) in a meta-analysis of 59 investigations involving 1451 athletes from dynamic (e.g., running), static (e.g., weight lifting) and combined sports (e.g., cycling, rowing) who revealed that there were no significant differences between athletes and control participants with regards to resting EF or FS.

However, other investigators have demonstrated that resting systolic performance may be improved after endurance training (16, 46, 57, 96). However, the majority of measures of systolic function including EF and FS are afterload and preload dependent (84). When these measures are abnormal corrections for afterload and preload must be made (7). According to Colan (7) these differences in resting systolic function are likely the result of changes in preload and/or afterload and do not necessarily reflect changes in myocardial contractility.

The effect of endurance training on systolic function during exercise is also equivocal. Investigators have shown that the measures of EF, and the SBP/ESV ratio during exercise conditions are not significantly different after training (61). This is supported by the present investigation wherein both EF and the SBP/ESV were not significantly altered by either training program.

However, others have revealed that exercise measures of EF, FS and/or the SBP/ESV ratio are significantly improved after endurance training (20, 66, 90). Also, investigators have revealed that other measures of systolic function are improved after endurance training. For instance, an increase in systolic contractile function during peak exercise (as evaluated by the relationship of FS to end-systolic wall stress) was observed after only 10 days of training (66). Several authors have shown that the rate of systolic emptying (as evaluated by PER) during exercise is improved by endurance training (33, 52). In the present investigation, both continuous and interval training resulted in a significant improvement in the PER response to incremental exercise. Therefore, although many indices of systolic function during exercise may not change with endurance training, certain systolic parameters may be enhanced by endurance training.

Left Ventricular Diastolic Function

There was no significant change in resting LV diastolic function (in the supine or semi-recumbent positions, respectively) as evaluated by Doppler echocardiography and radionuclide ventriculography. This is consistent with the findings of several investigations (22, 24, 37, 54, 67, 69, 70, 85, 92), but is contrary to the work of others (8, 18, 27, 53, 62, 63, 91). The reasons for these discrepancies are unclear, but may be related to differences in measurement procedures, testing protocol and/or training regimes.

Improvements in diastolic filling during exercise are a common finding in the literature (18, 33, 52, 53, 63, 69). The augmentation in diastolic filling is thought to compensate for the decrease in the diastolic period during exercise resulting from tachycardia, such that SV is not impaired (33, 52, 63). In the present investigation, there were large increases in diastolic filling during exercise (as determined by peak filling rate) after both continuous and interval training.

The increased diastolic filling after training allowed for an improvement in EDV throughout incremental exercise. As such, after both training programs the participants were able to fill and empty their ventricles to a greater extent. Very little change in ESV and myocardial contractility (i.e., the SBP/ESV ratio) occurred as a result of training. Therefore, the primary adaptation allowing SV to increase during exercise conditions was likely related to an increased ability to utilize the Frank-Starling mechanism during incremental exercise. This is supported by the research of Rerych et al. (81) who observed that endurance training resulted in a significant improvement in EDV, with a maintained heart rate and EF. As such, the authors concluded that endurance training results in an enhanced ability to use the Frank-Starling mechanism throughout exercise. This is supported by several investigations which indicate that the major difference between endurance-trained athletes and their sedentary counterparts is the enhanced capacity of the endurance athletes to utilize the Frank-Starling mechanism (33, 34, 52, 107).

However, it is important to note that the myocardial contractility and tachycardia still played a large role in the elevation in $\dot{Q}$ during the later stages of vigorous exercise. Training did result in an increased capacity to utilize the Frank-Starling mechanism (i.e., increased EDV), which allowed $\dot{Q}$ to reach higher levels than before training. However, the increase in SV (even after training) during the later stages of exercise in these untrained individuals remained largely due to myocardial contractility and tachycardia. This is evident by the small elevations in EDV during the later stages of vigorous exercise and large decreases in ESV. This finding is commonly seen in normally active and moderately trained individuals (as discussed in Chapter Three). Thus, although this short-term training increases the myocardium's ability to fill via the Frank-Starling effect, with little change in myocardial contractility, the $\dot{Q}$ during the later stages of exercise still remains dependent on myocardial contractility and tachycardia. This is contrary to the findings in highly trained endurance athletes (as discussed in Chapter Three) and may indicate that short term training does not elicit the myocardial adaptations seen after long term training.

Effects of Continuous Versus Interval Training on Left Ventricular Morphology

Endurance training has been associated with increased LV dimensions and mass and has been the topic of several reviews (28, 75). Endurance training has been associated with an increased LV cavity size and a slight increase in LV wall thickness (60, 68, 73-75, 97). This is generally believed to be the result of a chronic volume overload, leading to an increase in end-diastolic wall stress (28). In response to the increased end-diastolic wall stress, the myocardium is thought to experience eccentric hypertrophy to allow end-diastolic wall stress to be normalized (according to the Law of La Place).

The increased end-diastolic wall leading to ventricular hypertrophy is thought to result from prolonged exercise at an elevated venous return (i.e., high SV and $\dot{Q}$) and a reduced total peripheral resistance (75). The training-induced in BV may also further the volume loading effects of training. Therefore, training which augments $\dot{Q}$ and BV may lead potentially to an increase in LV morphology. Several cross-sectional investigations have observed a slight elevation in heart size in endurance athletes in comparison to untrained individuals (5, 30, 60, 70, 74, 97, 102). However, the findings from longitudinal investigations are equivocal, with some investigators reporting an improvement in LV morphology after endurance training (57), while others have observed no significant change in LV morphology after training (44, 82). In the present investigation, both continuous and interval training had no significant impact on LV dimensions. It is possible that the volume of training was not sufficient to elicit changes in myocardial morphology. Highly trained endurance athletes commonly train at moderate to high intensities, for hours per day, 5 to 7 days per weeks. Also, most competitive endurance athletes have been training for several years. The participants in this investigation were only required to exercise for up to 48 minutes, 3 days a week for 12 weeks. Thus, the lack of LV morphological adaptations was likely the result of an insufficient training stimulus. These findings also indicate that a large increase in cardiovascular fitness can occur without concomitant changes in LV morphology. It is also important to stress that the effects of genetics and natural selection of individuals with increased LV dimensions to endurance activities need to be considered.

Effects of Continuous Versus Interval Training on Ventilatory Thresholds

The ability to perform prolonged strenuous exercise is dependent on an individuals' $\dot{V}O_2$max and to his/her "anaerobic threshold." Skinner and McLellan (95) proposed a two component model for ventilatory thresholds, where two distinct breakaway points in the ventilatory response to exercise occur. We chose to utilize this model for our investigation, wherein AerT was determined as the breakpoint in the relationship between $\dot{V}_E/\dot{V}O_2$ over time and AnT was determined as the breakpoint in the relationship between $\dot{V}_E/\dot{V}CO_2$ over time.

A paucity of information exists regarding the effects of interval versus continuous training on ventilatory thresholds. However, previous investigators have postulated that interval training would be more beneficial for delaying the onset of anaerobiosis (58, 78). The improvements in ventilatory thresholds after interval training are thought to be the result of the biochemical adaptations in skeletal muscle brought about by the high training intensity (58, 78).

In the present investigation, AerT and AnT were significantly increased after both continuous and interval endurance training. The changes in ventilatory thresholds were similar between the training groups and were associated with concomitant changes in $\dot{V}O_2$max. Therefore, the percentage (or relative) AerT and AnT were not significantly changed as a result of training. The finding of no differences between groups in the magnitude of enhancements in ventilatory thresholds was similar to that of other investigators examining the effects of interval versus continuous training (71). However, other investigators have reported changes in ventilatory thresholds are greater after interval training in comparison to continuous training (78). The reasons for these discrepancies are unclear, but may be related to differences in participants' initial ventilatory threshold values and/or differences in training protocols. For instance, the investigation of Poole and Gaesser (78) utilized an interval program of 10 repetitions of supramaximal 2 min exercise (~105% $\dot{V}O_2$max) interspersed with 2 min periods of rest. It is possible that the higher intensity exercise may have affected ventilatory threshold to greater extent than the work intensity utilized in the present investigation (i.e., 90% $\dot{V}O_2$max). However, Overend et al. (71) also reported that two forms of interval training, termed low power output (i.e., 3 min exercise at 100% $\dot{V}O_2$max and 2 min at 50% $\dot{V}O_2$max) and high power output (i.e., 30 sec at 120% $\dot{V}O_2$max with 30 sec at 40%

$\dot{V}O_2$max), resulted in similar improvements in ventilatory threshold in comparison to continuous training. Overend et al. (71) postulated that the discrepancies may be related to the low baseline ventilatory threshold levels of the participants in the investigation of Poole and Gaesser (78).

The lack of change in relative ventilatory thresholds is similar to that observed by other investigators (64, 71) and indicates that the improvements in ventilatory thresholds are associated with concomitant changes in $\dot{V}O_2$max. This is contrary to other research which indicates that ventilatory thresholds may change independent from $\dot{V}O_2$max as a result of endurance training (86).

Myocardial Oxygen Consumption

The measurement of $M\dot{V}O_2$ in the healthy untrained, healthy trained, and patients with heart failure has recently been evaluated (2, 50) (Chapter Three). However, to our knowledge no information exists regarding the effects of continuous versus interval training on $M\dot{V}O_2$. In the present investigation, endurance training resulted in a significant elevation in calculated $M\dot{V}O_2$, which was largely the result of an increase in SW. The elevation in $M\dot{V}O_2$ was similar after both continuous and interval training. However, estimated $M\dot{V}O_2$ using the measures of BP and heart rate (i.e., RPP) was not significantly changed as a result of training. This may indicate that the RPP, despite its relationship with $M\dot{V}O_2$, is not sensitive enough of a measure to determine small changes in $M\dot{V}O_2$ resulting from short-term training. Further research is required to evaluate this hypothesis.

The calculated $M\dot{V}O_2$ before and after training increased 4- to 5-fold from rest to maximal exercise. This is quite similar to the findings in healthy individuals (50) and endurance-trained athletes (Chapter Three). Also, similar to the findings of other investigators (50) (Chapter Three) the efficiency of the myocardium was relatively maintained from rest to exercise conditions.

Volume-regulatory Hormones

As previously outlined, the exercise-induced hypervolemia is of great importance for the enhanced cardiovascular function observed after endurance training. Therefore, the maintenance of an elevated BV for prolonged periods of time would be beneficial for aerobic performance.

Several theories have been put forward to explain the volume expansion that occurs as a result of training. Convertino et al. (11) postulated that two mechanisms are associated with exercise-induced hypervolemia including an increased plasma protein content (i.e., albumin) and an increased retention of water and sodium. However, the expansion of total body water and vascular volumes are likely to elevate intravascular pressures leading to the stimulation of volume-regulatory reflex mechanisms (e.g. atrial natriuretic peptide) which serve to return BV to normal levels (13, 31). Several investigators have shown the ability of endurance-trained individuals to maintain a chronically expanded BV (9, 33, 52). Thus, compensatory mechanisms must be at play allowing an expanded BV to be maintained over a training regimen.

The impact that volume-regulating hormones have on the induction and the maintenance of hypervolemia remains unclear. Several investigators have explored the impact of changes in the volume-regulatory hormones on exercise-induced hypervolemia. Convertino and coworkers (11) postulated that the maintenance of an elevated BV is the result of a continual stimulation of the renin-angiotensin-aldosterone systems. Luetkemeier et al. (55) also revealed that at an aldosterone inhibitor (i.e., spironolactone) attenuated the increase of PV expansion after 3 days of cycling. They postulated that approximately two fifths of the exercise-induced PV expansion was the result of an increased aldosterone activity. Therefore, the volume-regulatory hormones may play a large role in the training-induced BV expansion. However, it is generally believed that endurance training does not significantly affect resting concentrations of renin-angiotensin, aldosterone, vasopressin or atrial natriuretic peptide (103).

In the present investigation, we examined the effects of short-term continuous and interval training on resting levels of atrial natriuretic peptide. Atrial natriuretic peptide is secreted by the atria in response to atrial stretch (26). As such, the exercise-induced hypervolemia and increased ventricular filling (i.e., EDV) as a result of training would be expected to increase the secretion of atrial natriuretic peptide. However, in the present investigation, similar to other investigations (93), no significant changes in the resting plasma concentration or total content of atrial natriuretic peptide were observed after training. As such, it appears as if both continuous and interval training do not significantly alter resting levels of atrial natriuretic peptide, even after accounting for changes in PV.

Aldosterone is a major determinant of tubular sodium reabsorption and as such is involved in both water and sodium conservation. As previously highlighted, researchers have revealed that aldosterone plays a significant role in the induction of BV expansion. However, training generally does not change resting concentrations of aldosterone (29, 103). In the present investigation, there was no significant change in resting concentrations or the total amount of aldosterone. Aldosterone did tend to increase throughout training. However, there was large inter-individual variation in resting aldosterone levels, which make further conclusions regarding the training-induced changes in aldosterone difficult to make.

The resting concentration of angiotensin II is generally thought to be unaffected by endurance training (103). In the present investigation, the early increase in PV was associated with a significant increase in angiotensin II. After week one, angiotensin II was reduced progressively until week 12 where it reached a level that was below baseline. This may indicate that the early increases in vascular volumes are related to changes in the renin-angiotensin system. However, the overall changes in the volume-regulatory hormones were small and could not explain the large increases in vascular volumes that occurred throughout training. These results may indicate that the post-exercise BV expansion is only partially due to the exercise-induced changes in the volume-regulatory hormones (23).

The results from this investigation also are indicative of the importance of both intensity and duration of exercise on adaptations in hormones involved in volume regulation, since both training programs resulted in similar changes. However, further investigation is required to evaluate these hypotheses.

Summary

Continuous and interval training result in significant improvements in vascular volumes. The early expansion of BV is associated with an increase in hormones involved in anti-diuresis. The increase in BV in both training groups accounted for a significant portion of the enhancement in cardiovascular function that occurred with training. The improvement in cardiovascular function after training is directly related to central adaptations including an increased ability to utilize the Frank-Starling mechanism. Twelve weeks of continuous or interval training does not provide a sufficient stimulus for changes in LV morphology and/or resting LV function.

Table 4.1. Participant characteristics at baseline (Mean ± SD).

Measurement	**Interval (n = 8)**	**Continuous (n = 8)**	**Control (n =8)**	**All Groups (n = 24)**
Age (yr)	30.6 ± 6.0	29.5 ± 3.5	28.9 ± 3.3	29.7 ± 4.2
Height (cm)	176.4 ± 7.0	176.4 ± 5.4	175.1 ± 6.1	176.2 ± 5.7
Weight (kg)	82.5 ± 11.1	85.6 ± 24.6	81.3 ± 10.4	83.8 ± 16.4
$\dot{V}O_2$max (L·min^{-1})	3.22 ± 0.72	3.26 ± 0.71	3.12 ± 0.50	3.51 ± 0.75
$\dot{V}O_2$max (mL·kg^{-1}·min^{-1})	39.2 ± 8.3	39.2 ± 6.4	39.0 ± 7.8	39.1 ± 7.2
Blood Volume (mL)	5109 ± 748	5587 ± 1722	5204 ± 634	5300 ± 1113
Blood Volume (mL·kg^{-1})	62.4 ± 9.6	65.6 ± 11.1	64.6 ± 7.9	64.2 ± 9.3
Haematocrit (%)	43 ± 2	43 ± 2	44 ± 2	43 ± 3
Haemoglobin (g·L^{-1})	161 ± 139	156 ± 109	148 ± 119	155 ± 129

Table 4.2. Changes in resting blood volume over the 12-week training period (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
Blood Volume (mL)	5109 ± 748	5519 ± 816	5741 ± 434	5332 ± 1689	5914 ± 1724	5765 ± 1826	5204 ± 634	5182 ± 861
Blood Volume (%mL)	0	8.0 ± 5.4†	9.8 ± 5.5†	0	12.0 ± 7.4†	10.5 ± 9.3*†	0	-0.6 ± 9.3
Blood Volume ($mL \cdot kg^{-1}$)	62.4 ± 9.6	67.0 ± 9.4	67.2 ± 9.2	65.6 ± 11.1	74.2 ± 11.3	73.8 ± 11.3	64.6 ± 7.9	64.1 ± 10.6
Blood Volume ($\%mL \cdot kg^{-1}$)	0	7.7 ± 5.9†	10.5 ± 6.4†	0	11.8 ± 7.0†	13.6 ± 8.3†	0	-0.9 ± 8.8
Plasma Volume (mL)	3101 ± 493	3298 ± 491	3469 ± 265	3387 ± 1009	3764 ± 1044	3453 ± 1007	3135 ± 393	3146 ± 503
Plasma Volume (%mL)	0	6.6 ± 6.7†	10.1 ± 9.7†	0	12.9 ± 8.4†	9.9 ± 8.8†	0	0.4 ± 10.3
Plasma Volume ($mL \cdot kg^{-1}$)	38.0 ± 6.6	40.1 ± 5.7	40.7 ± 5.4	39.8 ± 6.4	44.6 ± 7.6	44.5 ± 7.4	38.9 ± 4.9	38.9 ± 6.3
Plasma Volume ($\%mL \cdot kg^{-1}$)	0	6.4 ± 7.3†	10.9 ± 11.2†	0	13.3 ± 8.9†	12.9 ± 7.7†	0	0.1 ± 9.4
Red Cell Volume (mL)	2009 ± 268	2220 ± 340	2272 ± 253	2102 ± 716	2296 ± 720	2313 ± 831	2070 ± 341	2036 ± 393
Red Cell Volume (%mL)	0	10.3 ± 6.4†	9.7 ± 7.4†	0	10.8 ± 9.6†	11.6 ± 12.0†	0	-1.7 ± 8.7
Red Cell Volume ($mL \cdot kg^{-1}$)	24.4 ± 3.1	27.0 ± 4.0	26.6 ± 4.4	26.1 ± 5.1	28.7 ± 4.4	29.3 ± 4.4	25.7 ±4.3	25.2 ± 4.7
Red Cell Volume ($\%mL \cdot kg^{-1}$)	0	10.0 ± 6.6†	10.3 ± 6.4†	0	11.1 ± 8.7†	14.7 ± 11.2†	0	-2.0 ± 8.4

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; %, refers to the percent change in comparison to baseline; †, main effect for training in comparison to PRE.

Table 4.3. Changes in pre-exercise cardiorespiratory responses as a result of endurance training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
HR (beats·min^{-1})	76 ± 9	69 ± 4	76 ± 6	65 ± 4	67 ± 7	73 ± 13	82 ± 16	74 ± 10
VO_2 (mL·kg^{-1}·min^{-1})	4.11 ± 1.01	4.17 ± 1.24	3.82 ± 1.60	4.50 ± 0.89	4.97 ± 0.66	4.88 ± 1.68	4.75 ± 1.36	4.68 ± 0.47
SBP (mmHg)	124 ± 13	126 ± 12	124 ± 18	130 ± 12	120 ± 6	132 ± 5	132 ± 5	122 ± 8
DBP (mmHg)	84 ± 6	86 ± 4	87 ± 7	84 ± 5	82 ± 6	88 ± 8	82 ± 8	84 ± 6
MAP (mmHg)	98 ± 8	99 ± 5	99 ± 11	99 ± 6	94 ± 5	102 ± 5	96 ± 9	96 ± 5
V_E (L·min^{-1})	13.4 ± 3.3	12.9 ± 2.8	11.1 ± 3.9	16.2 ± 5.8	17.3 ± 4.9	14.2 ± 2.9	13.1 ± 3.8	12.5 ± 2.6
Oxygen Pulse (mL·beat^{-1})	4.6 ± 1.4	5.2 ± 2.0	4.4 ± 1.9	5.7 ± 1.3	6.2 ± 1.4	5.2 ± 1.4	4.9 ± 1.7	5.2 ± 1.3

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; HR, heart rate; VO_2max, maximal oxygen consumption; SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure; V_E, minute ventilation.

Table 4.4. Changes in maximal cardiorespiratory responses to incremental exercise as a result of endurance training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
HR (beats·min^{-1})	176 ± 8	177 ± 11	183 ± 10	181 ± 13	179 ±14	188 ± 12	186 ±9	185 ± 6
VO_2max (mL·kg^{-1}·min^{-1})	39.2 ± 8.3	44.7 ± 8.6†	47.3 ±12.7†	39.2 ± 6.4	46.6 ± 6.9†	49.6 ± 5.8†	39.0 ± 7.8	38.8 ± 7.0
SBP (mmHg)	204 ± 26	202 ± 24	211 ± 22	213 ± 25	214 ± 11	204 ± 20	209 ± 23	200 ± 28
DBP (mmHg)	83 ± 8	80 ± 11	81 ± 13	83 ± 8	76 ± 13	81 ± 8	83 ± 12	89 ± 8
MAP (mmHg)	123 ± 10	121 ± 13	124 ± 14	126 ± 8	122 ± 9	122 ± 8	126 ± 13	126 ± 13
V_E (L·min^{-1})	122 ± 21	153 ± 38†	153 ± 33†	130 ± 30	153 ± 28†	166 ± 15†	139 ± 33	132 ± 26
Oxygen Pulse (mL·beat^{-1})	18 ± 4	21 ± 4†	22 ± 6	18 ± 5	22 ± 4†	21 ± 5	17 ± 3	17 ± 3

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; HR, heart rate; VO_2max, maximal oxygen consumption; SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure; V_E, minute ventilation;,†, main effect for training in comparison to PRE.

Table 4.5. Changes in ventilatory thresholds and peak power output as a result of endurance training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
VO_2 @ AerT ($mL \cdot kg^{-1} \cdot min^{-1}$)	19.4 ± 3.8	22.1 ± 5.5	26.4 ± 4.8†	20.9 ± 3.7	24.1 ± 5.4	26.2 ± 4.3†	19.4 ± 2.7	19.2 ± 3.2
AerT (%max)	52.4 ± 8.5	52.6 ± 11.9	57.5 ± 11.1	53.4 ± 6.0	52.2 ± 10.4	53.0 ± 4..0	51.1 ± 5.8	49.8 ± 6.3
VO_2 @ AnT ($mL \cdot kg^{-1} \cdot min^{-1}$)	25.9 ± 5.8	31.1 ± 5.2†	32.6 ± 5.9†	24.2 ± 4.3	32.0 ± 5.3†	32.8 ± 2.1†	25.1 ± 5.0	23.9 ± 4.3
AnT (%max)	68.5 ± 2.6	73.9 ± 9.0	70.5 ± 8.4	64.3 ± 3.7	69.1 ± 8.4	66.7 ± 9.2	65.9 ± 7.9	61.6 ± 6.7
Peak Power Output (Watts)	208 ± 47	261 ± 74†	305 ± 67†	226 ± 56	243 ± 67†	291 ± 71†	206 ± 29	229 ±39

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; VO_2 @ AerT, oxygen consumption at the aerobic threshold (AerT); VO_2 @ AnT, oxygen consumption at the anaerobic threshold (AnT); †, main effect for training in comparison to PRE.

Table 4.6. Changes in pre-exercise measures of cardiac function as a result of endurance training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
EF (%)	0.57 ± 0.08	0.62 ± 0.07	0.59 ± 0.10	0.55 ± 0.12	0.54 ± 0.09	0.58 ± 0.08	0.49 ± 0.03	0.52 ± 0.06
Q (L·min^{-1})	7.8 ± 2.7	9.4 ± 4.3	8.4 ± 2.0	7.3 ± 1.6	7.5 ± 1.7	8.6 ± 0.8	6.8 ± 1.0	6.3 ± 2.0
SV (mL·beat^{-1})	104 ± 34	134 ± 51	112 ± 29	108 ± 15	111 ± 25	121 ± 9	87 ± 22	85 ± 29
EDV (mL·beat^{-1})	173 ± 56	206 ± 73	179 ± 34	187 ± 31	194 ± 32	200 ± 36	165 ± 36	151 ± 38
ESV (mL·beat^{-1})	69 ± 29	72 ± 29	67 ± 21	79 ± 32	83 ± 22	80 ± 30	79 ± 17	67 ± 12
TPE (sec)	0.16 ± 0.05	0.17 ± 0.06	0.15 ± 0.04	0.24 ± 0.05	0.16 ± 0.07	0.15 ± 0.07	0.16 ± 0.05	0.16 ± 0.06
TPF (sec)	0.19 ± 0.05	0.15 ± 0.03	0.17 ± 0.02	0.17 ± 0.05	0.21 ± 0.13	0.19 ± 0.04	0.18 ± 0.05	0.20 ± 0.06
PER (mL·sec^{-1})	550 ± 122	732 ± 311	686 ± 242	538 ± 118	646 ± 155	660 ± 82	487 ± 115	611 ± 439
PFR (mL·sec^{-1})	432 ± 173	641 ± 258	536 ± 137	474 ± 215	492 ± 137	452 ± 113	388 ± 80	448 ± 245
SBP/ESV (mmHg·mL^{-1})	2.1 ± 0.8	2.0 ± 0.8	2.0 ± 0.7	1.9 ± 0.8	1.5 ± 0.3	1.8 ± 0.9	1.6 ± 0.5	1.9 ± 0.3

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; EF, ejection fraction; Q, cardiac output; SV, stroke volume; EDV, end-diastolic volume; ESV, end-systolic volume; TPE, time to peak ejection; TPF, time to peak filling; PER, peak ejection rate; PFR, peak filling rate; SBP/ESV, ratio of systolic blood pressure to end-systolic volume; a-$\bar{v}DO_2$, arterio-venous oxygen difference.

Table 4.7. Changes in cardiac function during maximal exercise as a result of endurance training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
EF (%)	0.74 ± 0.08	0.73 ± 0.07	0.74 ± 0.07	0.77 ± 0.08	0.74 ± 0.07	0.78 ± 0.04	0.74 ± 0.09	0.77 ± 0.10
Q (L·min^{-1})	22.6 ± 7.0	38.0 ± 10.5†	29.6 ± 10.0†	26.0 ± 7.6	32.1 ± 5.7†	36.7 ± 8.0†	23.7 ± 5.5	27.4 ± 7.6
SV (mL·beat^{-1})	130 ± 38	212 ± 54†	165 ± 56†	145 ± 44	193 ± 38†	204 ± 49†	129 ± 36	159 ± 44
EDV (mL·beat^{-1})	174 ± 51	282 ± 70†	214 ± 64	190 ± 48	254 ± 49†	252 ± 58	180 ± 57	202 ± 53
ESV (mL·beat^{-1})	45 ± 23	70 ± 25	50 ± 18	44 ± 16	61 ± 24	48 ± 14	47 ± 31	43 ± 21
TPE (sec)	0.078 ± 0.012	0.079 ± 0.016	0.095 ± 0.018	0.082 ± 0.014	0.087 ± 0.014	0.077 ± 0.010	0.083 ± 0.004	0.094 ± 0.010
TPF (sec)	0.100 ± 0.030	0.084 ± 0.019	0.080 ± 0.017	0.086 ± 0.009	0.102 ± 0.020	0.087 ± 0.018	0.083 ± 0.223	0.097 ± 0.020
PER (mL·sec^{-1})	1557 ± 393	2687 ± 884†*	1872 ± 733†*	1752 ± 683	2055 ± 563†*	2723 ± 930†*	1511 ± 379	1809 ± 609
PFR (mL·sec^{-1})	1890 ± 913	3556 ± 1664†	2392 ± 816†	2169 ± 712	2484 ± 590†	3057 ± 750†	1984 ± 365	2377 ± 572
SBP/ESV (mmHg·mL^{-1})	5.53 ± 2.52	3.30 ± 1.17	4.67 ± 1.58	5.53 ± 2.32	4.09 ± 1.70	4.87 ± 1.36	6.03 ± 2.87	5.7 ± 2.7

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; EF, ejection fraction; Q, cardiac output; SV, stroke volume; EDV, end-diastolic volume; ESV, end-systolic volume; TPE, time to peak ejection; TPF, time to peak filling; PER, peak ejection rate; PFR, peak filling rate; SBP/ESV, ratio of systolic blood pressure to end-systolic volume; a-$\bar{v}$DO$_2$, arterio-venous oxygen difference; †, main effect for training in comparison to PRE; *, training conditions are significantly different from one another.

Table 4.8. Changes in resting left ventricular morphology and function as assessed by M-mode echocardiography over the 12-week training period (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
RVIDd (mm)	23.8 ± 2.7	23.5 ± 3.2	22.8 ± 5.0	23.6 ± 6.0	23.9 ± 5.3	20.0 ± 3.3	22.1 ± 4.1	23.1 ± 5.6
LVIDd (mm)	52.0 ± 2.7	51.1 ±3.0	51.5 ± 3.4	54.4 ± 4.8	54.0 ± 5.4	54.6 ± 6.9	51.0 ± 4.6	49.8 ± 4.6
LVIDs (mm)	32.9 ± 3.1	31.6 ± 2.1	32.8 ± 1.9	33.8 ± 4.4	32.8 ± 4.6	33.4 ± 3.9	31.7 ± 2.7	29.8 ± 3.1
VSTd (mm)	8.8 ± 1.7	9.2 ± 1.4	9.9 ± 2.3	8.9 ± 1.2	9.4 ± 1.8	8.8 ± 1.5	9.5 ± 1.7	8.9 ± 1.3
VSTs (mm)	11.9 ± 2.2	12.2 ± 1.4	12.8 ± 2.0	11.7 ± 1.7	12.2 ± 1.8	12.4 ± 1.0	11.6 ± 1.4	11.6 ± 1.6
PWTd (mm)	8.4 ± 2.3	8.7 ± 1.5	8.4 ± 1.2	8.6 ± 1.3	8.5 ± 1.6	8.1 ± 1.4	8.1 ± 0.4	8.0 ± 1.2
PWTs (mm)	14.4 ± 1.8	14.9 ± 2.0	15.4 ± 2.1	15.9 ± 3.2	16.1 ± 2.6	15.1 ± 3.4	14.9 ± 1.8	13.9 ± 2.4
Aortic Diameter (mm)	22.7 ± 2.2	22.7 ± 1.7	23.1 ± 1.1	22.6 ± 2.3	22.8 ± 2.9	23.0 ± 2.9	22.7 ± 2.9	22.1 ± 1.4
FS (%)	51.3 ± 2.7	50.5 ± 3.0	50.9 ± 3.4	53.8 ± 4.8	53.4 ± 5.4	54.0 ± 6.9	50.3 ± 4.6	49.2 ± 4.5
LV Mass (g)	162 ± 55	165 ± 46	171 ± 45	181 ± 57	185 ± 70	174 ± 65	159 ± 32	144 ± 24
Wall Stress ($g \cdot cm^{-2}$)	121.2 ± 15.9	107.6 ± 13.5	121.6 ± 6.6	123.7 ± 15.0	117.3 ± 17.1	121.7 ± 22.4	120.1 ± 17.4	122.0 ± 14.2

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; RVIDd, right ventricular dimension during diastole; LVIDd, left ventricular dimension during diastole; LVIDs, left ventricular dimension during systole; VSTd, intraventricular septal wall thickness during diastole; VSTs, intraventricular septal wall thickness during systole; PWTd, posterior wall thickness during diastole; PWTs, posterior wall thickness during systole; FS, fractional shortening; LV mass, left ventricular mass.

Table 4.9. Changes in resting myocardial function as assessed by Doppler echocardiography over the 12-week training period (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
Peak E (m·sec^{-1})	73.3 ±12.0	76.0 ±8.7	77.0 ± 10.1	81.1 ±7.4	81.0 ±11.1	77.2 ± 8.4	78.8 ± 13.6	75.6 ± 17.3
Peak A (m·sec^{-1})	51.6 ± 9.3	45.6 ± 8.0	46.4 ± 9.1	46.3 ± 7.4	43.5 ± 7.5	51.2 ± 3.1	49.7 ± 6.7	43.1 ± 6.5
E/A Ratio	1.44 ± 0.24	1.72 ± 0.47	1.69 ± 0.27	1.80 ± 0.36	1.91 ± 0.43	1.51 ± 0.18	1.61 ± 0.34	1.74 ± 0.28
VTI (m·sec^{-1})	19.7 ± 1.6	21.7 ± 3.4	22.9 ± 2.9	27.2 ±	21.6 ± 3.9	22.6 ± 4.7	18.9 ± 3.5	19.0 ± 4.6
SV (mL·beat^{-1})	45.0 ± 6.8	44.0 ± 19.4	53.1 ± 8.5	60.2 ±	49.1 ± 9.8	52.4 ± 14.3	42.9 ± 9.9	42.3 ± 11.1
DT (sec)	0.555 ± 0.136	0.602 ± 0.129 †	0.652 ± 0.091	0.571 ± 0.141	0.731 ± 0.203 †	0.604 ± 0.132	0.573 ± 0.165	0.629 ± 0.100
LVET (sec)	0.298 ± 0.016	0.304 ± 0.020	0.304 ± 0.006	0.314 ± 0.022	0.313 ± 0.019	0.290 ± 0.022	0.301 ± 0.028	0.298 ± 0.032

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; Peak E, peak early filling velocity; Peak A, peak late filling velocity; E/A ratio; the ratio of early to late ventricular filling; VTI, velocity time integral; SV, stroke volume (mL); DT, diastolic filling time; LVET, left ventricular ejection time; †, main effect for training in comparison to PRE.

Table 4.10. Alterations in the volume regulatory hormones after training (Mean ± SD).

Measure	Interval Training			Continuous Training			Control	
	PRE	MID	POST	PRE	MID	POST	PRE	POST
Aldosterone ($\text{pg}\cdot\text{mL}^{-1}$)	82.7 ± 29.6	77.2 ± 29.8	87.4 ± 37.0	70.0 ± 25.4	80.4 ± 39.1	90.1 ± 46.1	73.6 ± 29.8	65.2 ± 22.4
Aldosterone (pg)	253759 ± 99126	255441 ± 109615	302637 ± 132551	225513 ± 77784	267315 ± 73220	300435 ± 136384	227271 ± 84865	206067 ± 82726
α-ANP ($\text{pg}\cdot\text{mL}^{-1}$)	26.3 ± 8.4	28.0 ± 8.0	23.3 ± 9.0	16.8 ± 4.1	30.4 ± 21.2	21.7 ± 9.6	24.4 ± 19.3	24.3 ± 17.2
α-ANP (pg)	81629 ± 31884	92254 ± 29417	80019 ± 28847	58758 ± 28537	117592 ± 89792	77379 ± 49916	78955 ± 67948	70204 ± 39777
Angiotensin II ($\text{pg}\cdot\text{mL}^{-1}$)	22.7 ± 10.4	19.3 ± 7.3	21.1 ± 10.4	21.8 ± 6.5	22.7 ± 4.0	19.4 ± 5.7	18.4 ± 14.0	18.1 ± 7.3
Angiotensin II (pg)	68376 ± 32064	62959 ± 24.2	71821 ± 37262	74224 ± 31184	84124 ± 22011	62823 ± 11367	57212 ± 45002	55483 ± 18295

PRE, pre-training; MID, six weeks of training; POST, twelve weeks of training; α-ANP, atrial natriuretic peptide.

Table 4.11. Relationship between vascular volumes and maximal aerobic power after endurance training.

Relative/Absolute Changes			Percent Changes		
Relative Volume	VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	VO_2max ($L \cdot min^{-1}$)	Percent Change	VO_2max ($\%mL \cdot kg^{-1} \cdot min^{-1}$)	VO_2max ($\%L \cdot min^{-1}$)
BV ($mL \cdot kg^{-1}$)	0.71*	0.43*	BV (%)	0.75*	0.73*
PV ($mL \cdot kg^{-1}$)	0.70*	0.38*	PV (%)	0.66*	0.64*
RCV ($mL \cdot kg^{-1}$)	0.67*	0.48*	RCV (%)	0.67*	0.67*

BV, blood volume; PV, plasma volume; RCV, red cell volume; %, percent changes in comparison to baseline; *, significant relationship between variables of interest ($p < 0.05$).

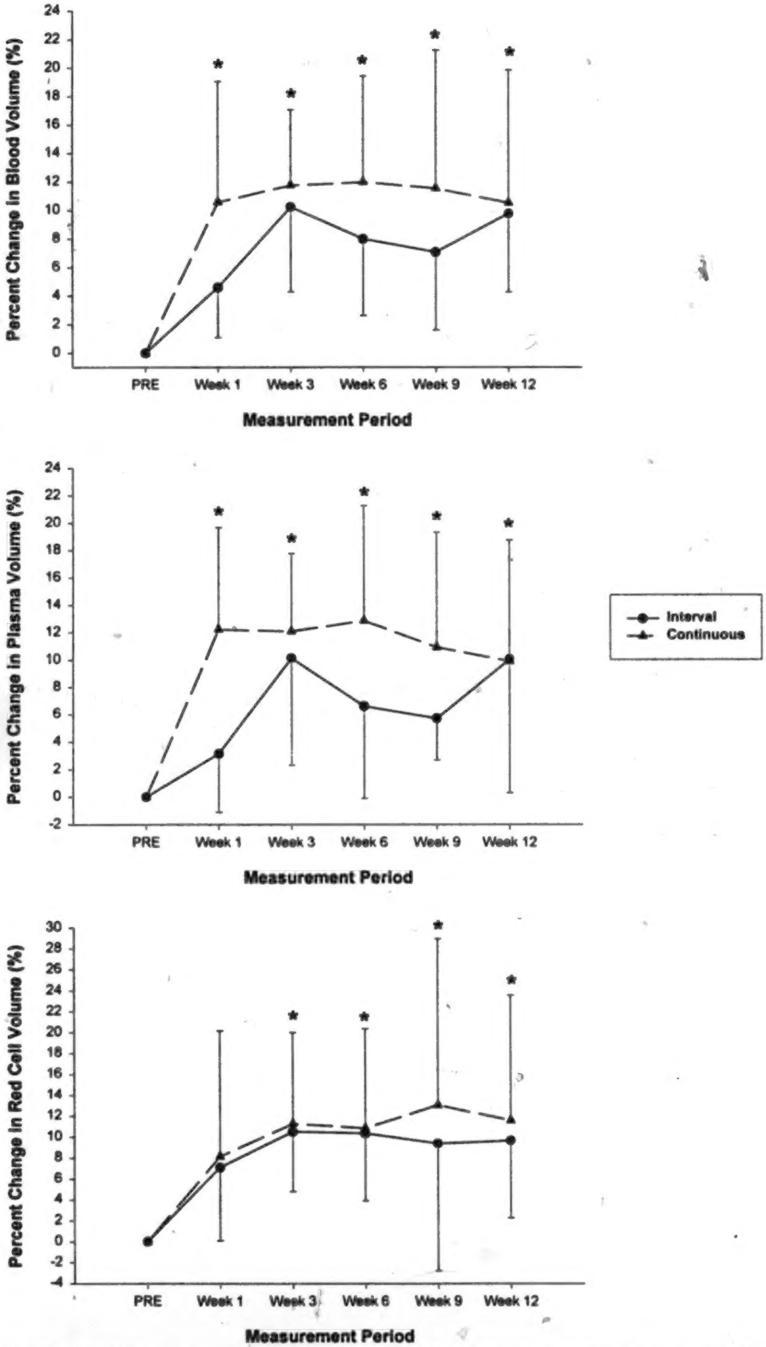


Figure 4.1. Percent changes in vascular volumes as a result of endurance training (Error Bars = SD). *, significantly different from PRE ($p < 0.05$).

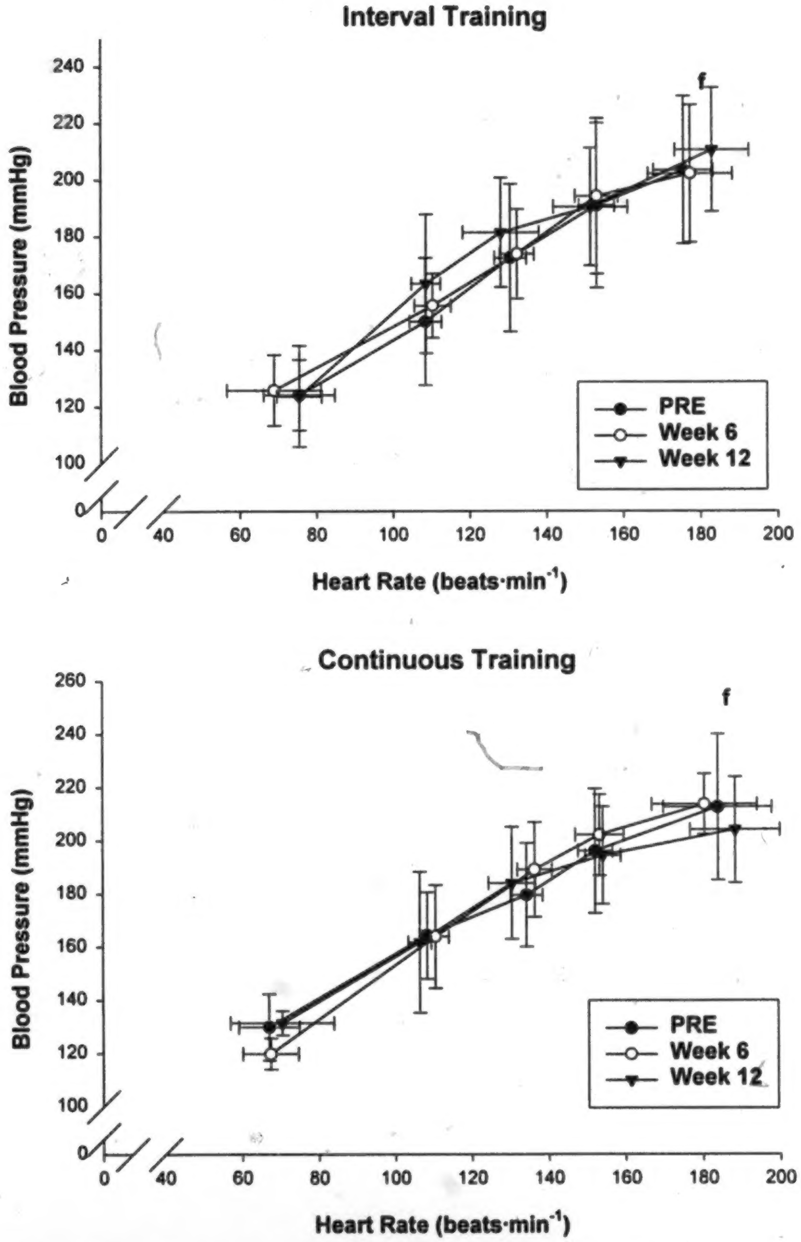
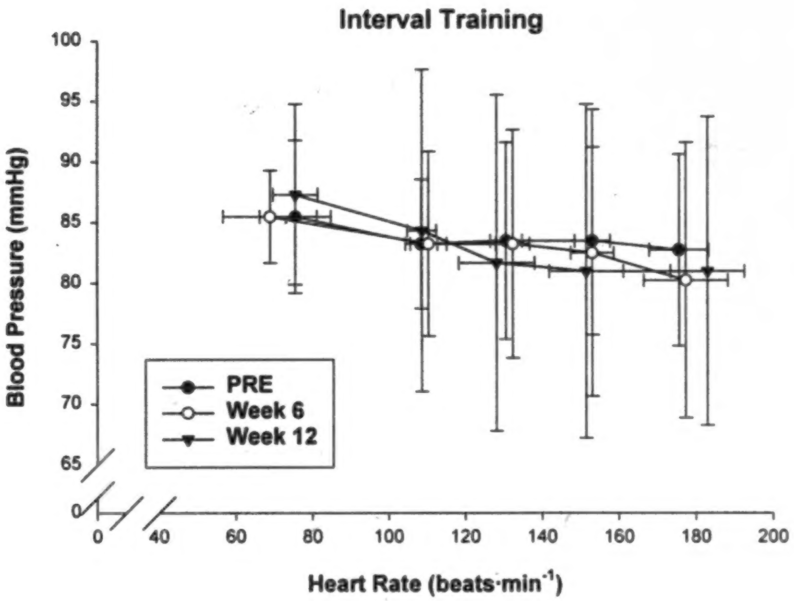


Figure 4.2. Effects of endurance training on systolic blood pressure during incremental exercise (Error Bars = SD). f, significant difference throughout exercise ($p < 0.05$).



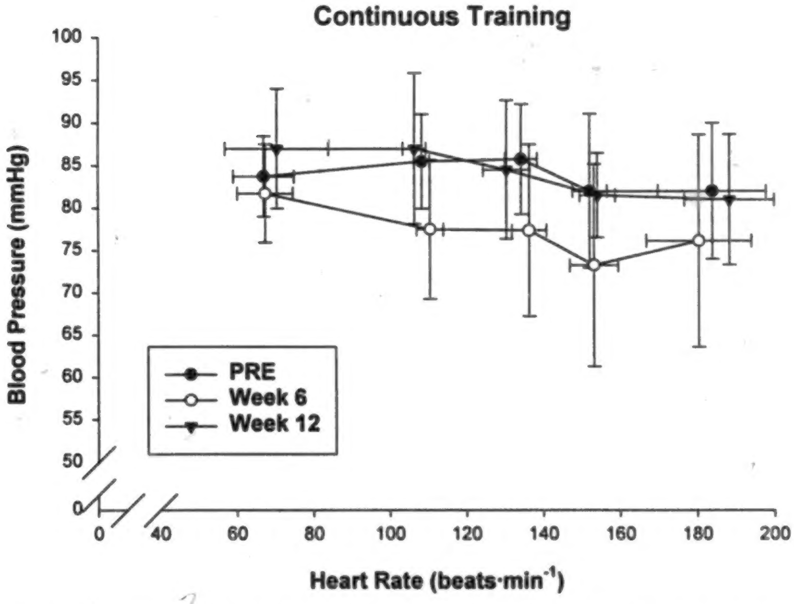


Figure 4.3. Effects of endurance training on diastolic blood pressure during incremental exercise (Error Bars = SD).

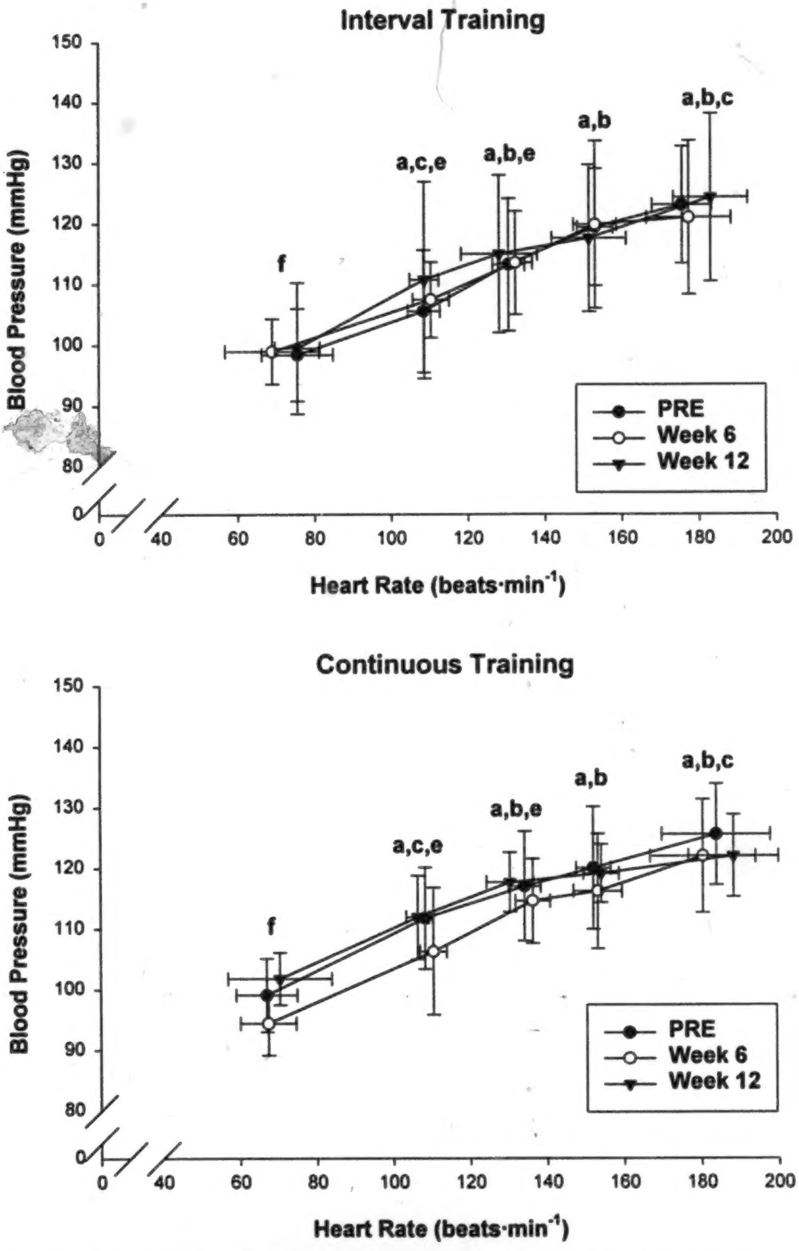


Figure 4.4. Effects of endurance training on mean arterial blood pressure during incremental exercise (Error Bars =SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, signficantly different from 150 beats.min-1;·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates ($p < 0.05$).

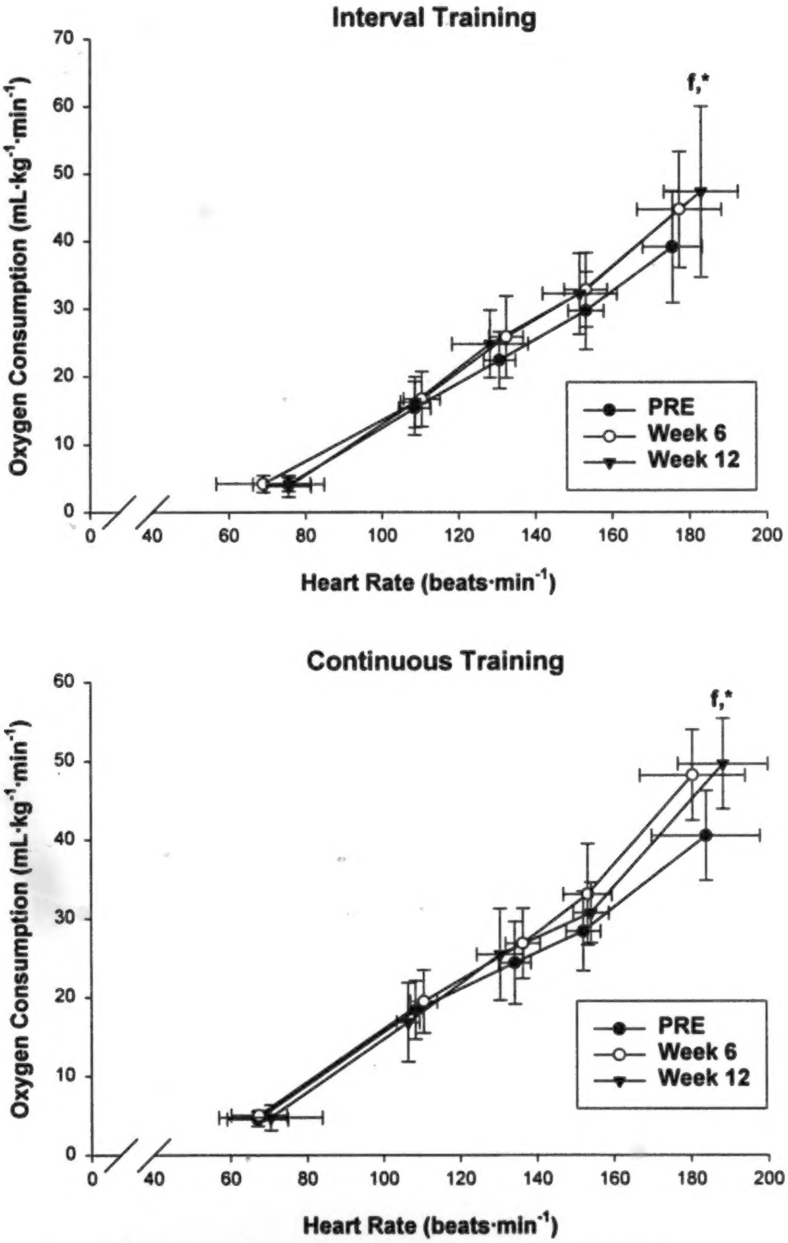


Figure 4.5. Effects of endurance training on oxygen consumption during incremental exercise (Error Bars = SD). f, significant difference throughout exercise; *, main effect for training after weeks six and 12 of training ($p < 0.05$).

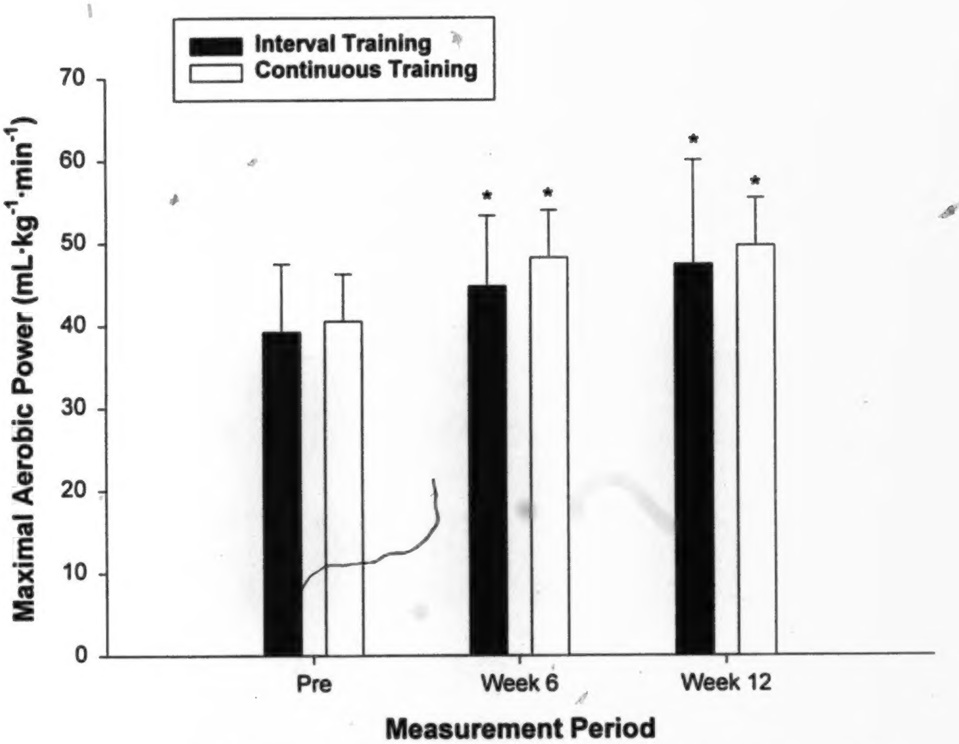


Figure 4.6. Effects of endurance training on maximal aerobic power (Error Bars = SD). *, significant difference in comparison to PRE ($p < 0.05$).

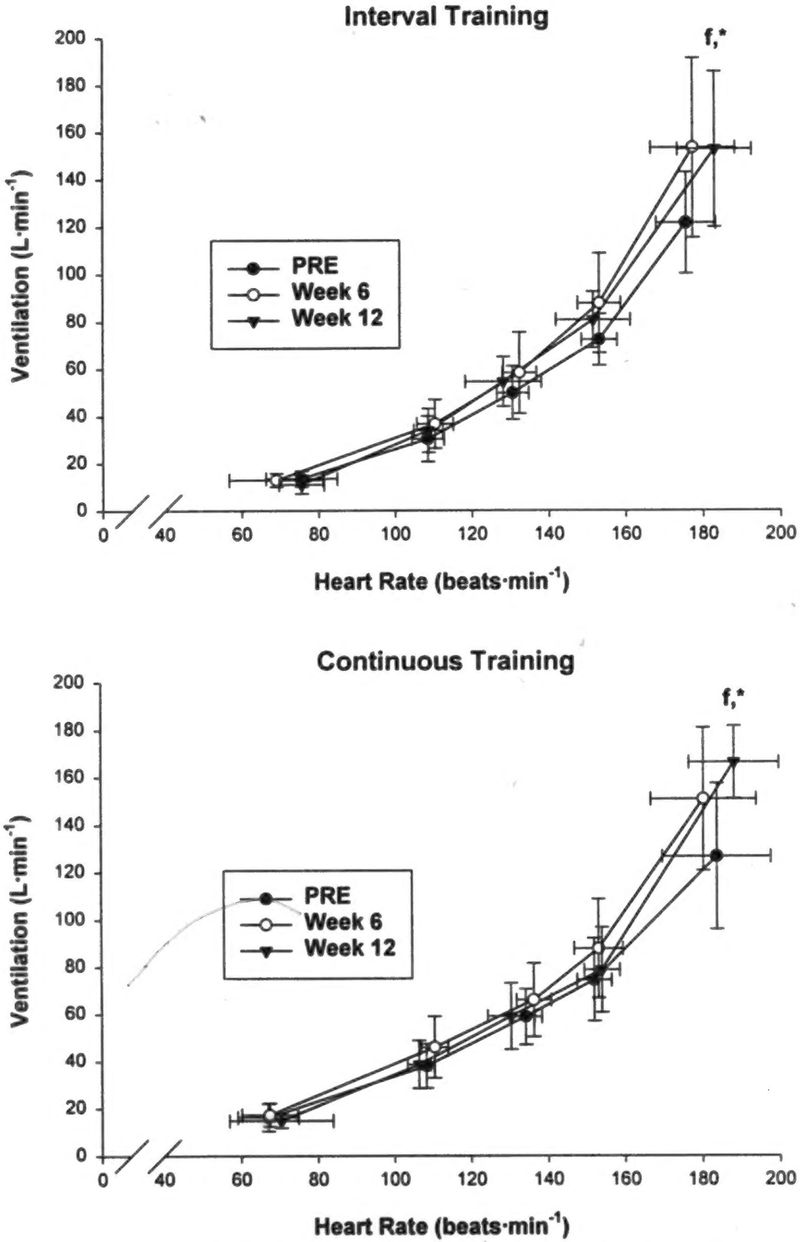


Figure 4.7. Effects of endurance training on minute ventilation during incremental exercise (Error Bars = SD). f, significant difference throughout incremental exercise; *, significant difference in comparison to PRE ($p < 0.05$).

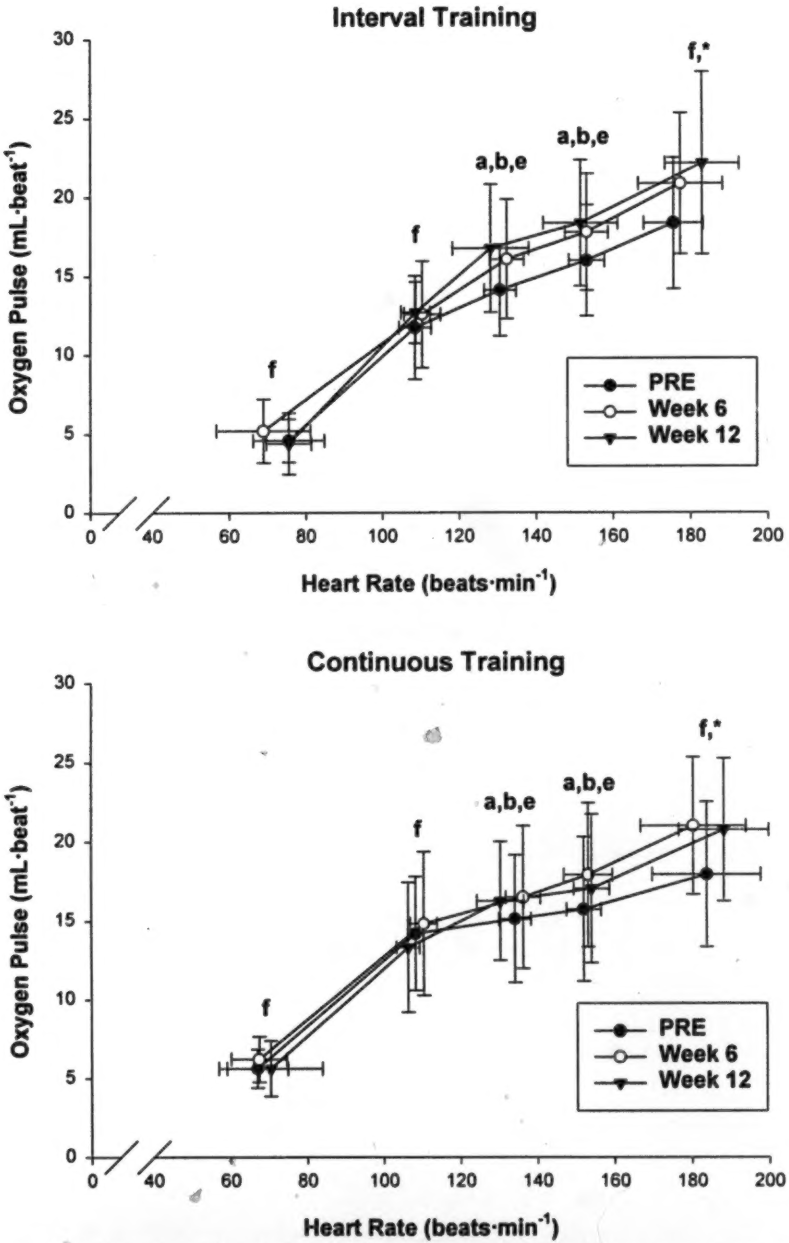


Figure 4.8. Effects of endurance training on oxygen pulse during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats.min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates; *, main effect for week six of training ($p < 0.05$).

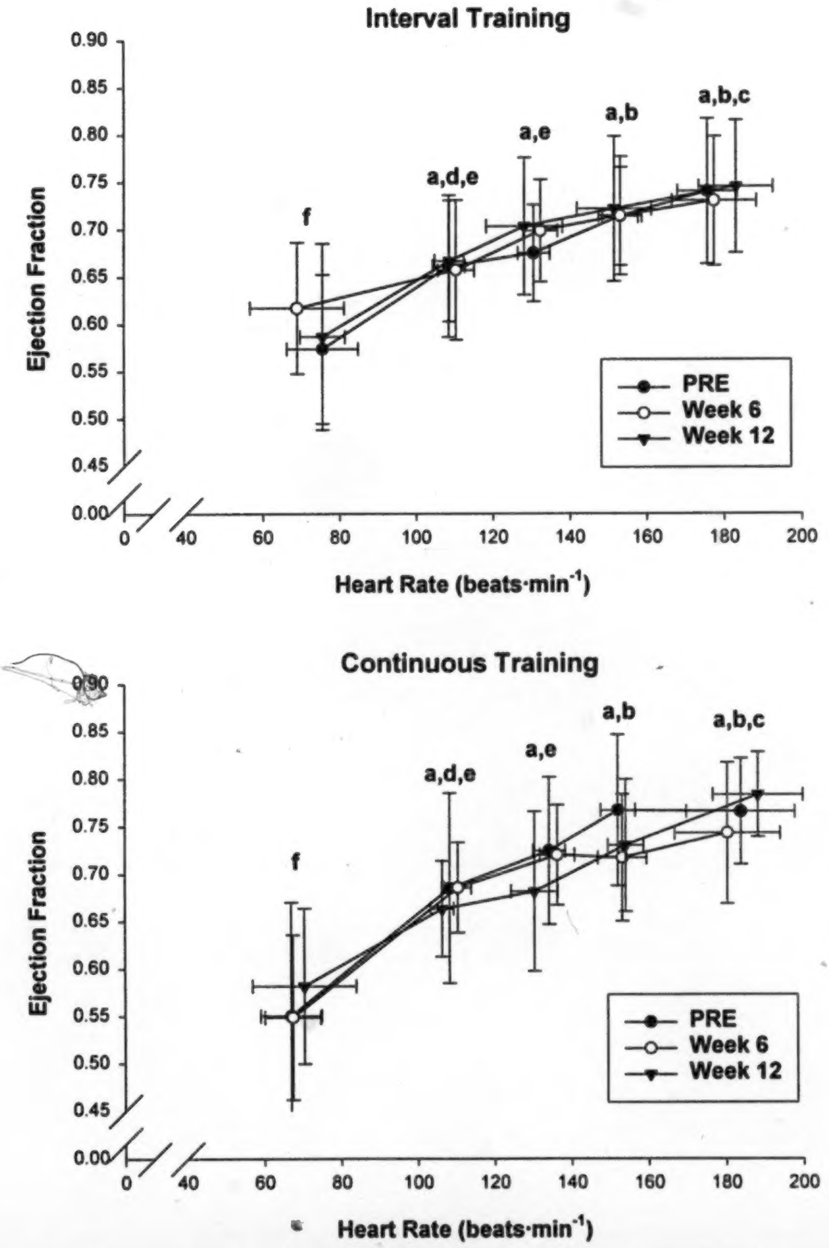


Figure 4.9. Effects of endurance training on ejection fraction during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates ($p < 0.05$).

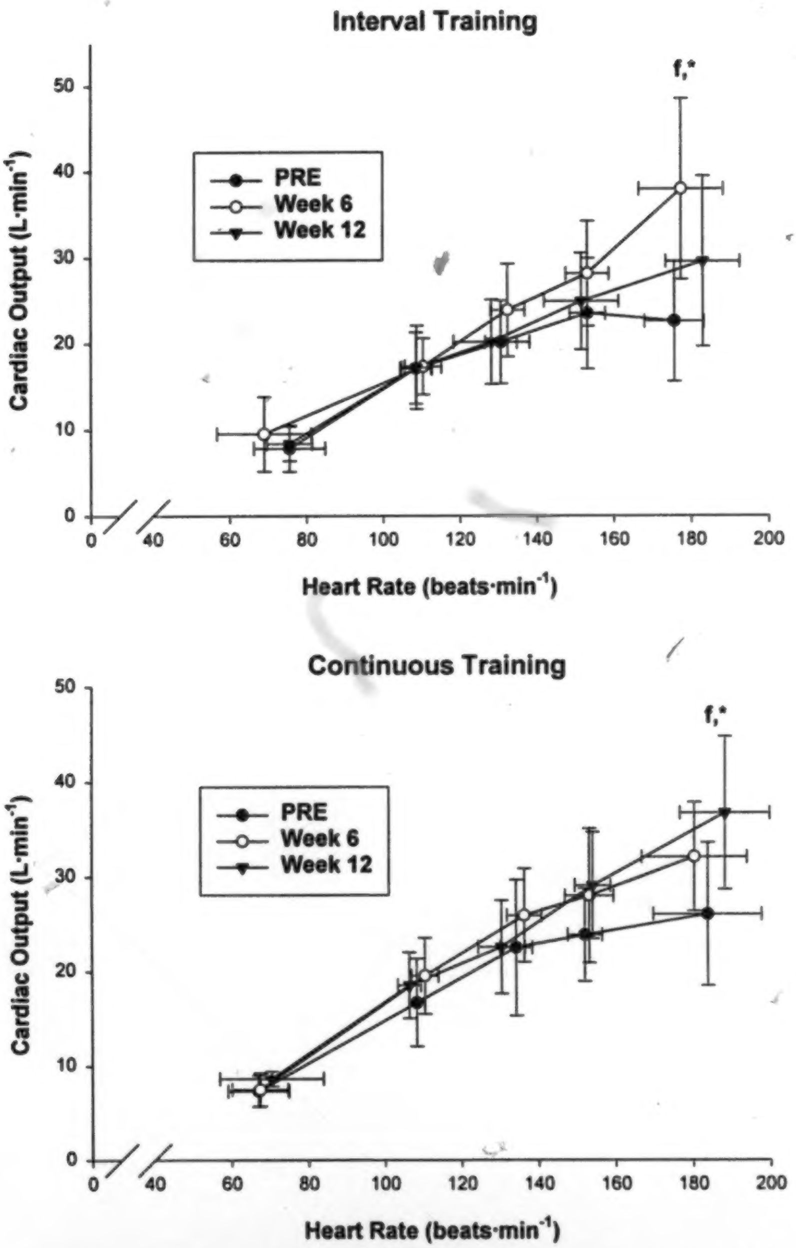


Figure 4.10. Effects of endurance training on cardiac output during incremental exercise (Error Bars = SD). f, significant difference throughout incremental exercise; *, main effect for training for weeks six and 12 of training; ($p < 0.05$).

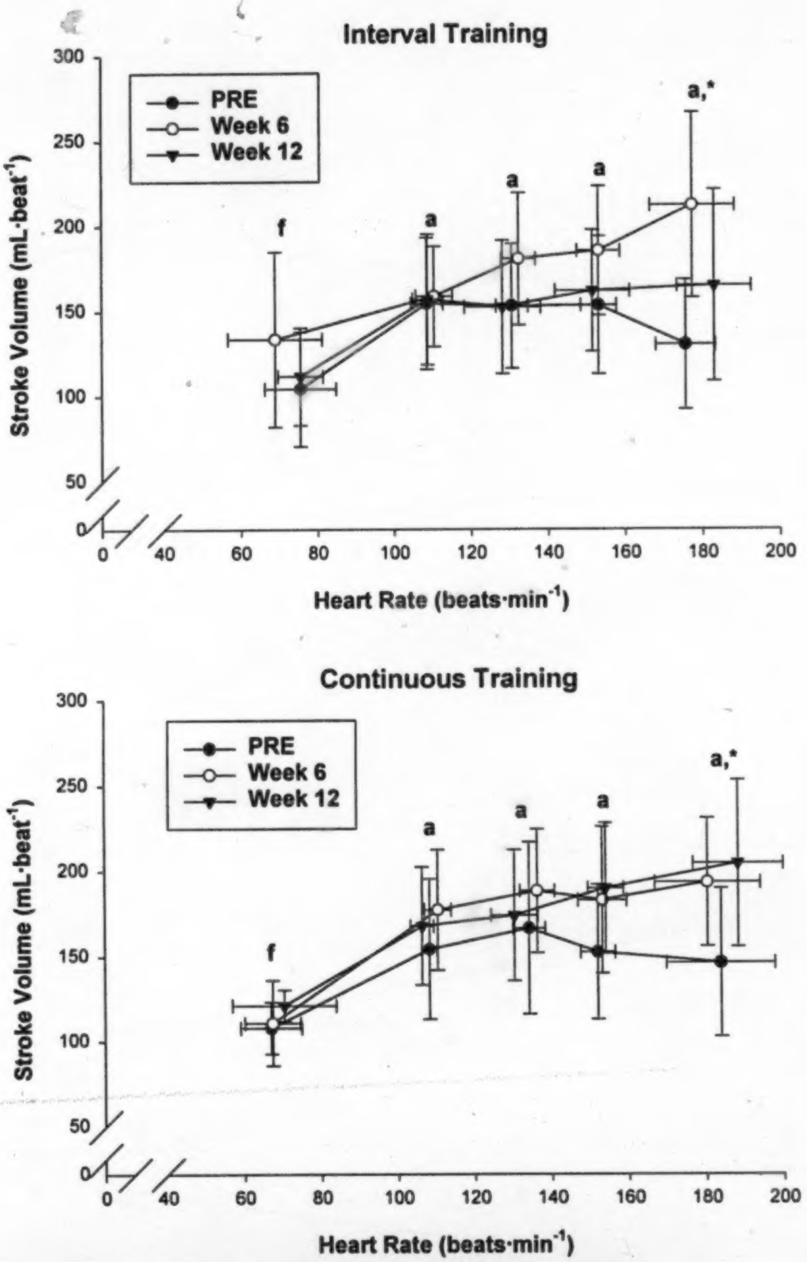


Figure 4.11. Effects of endurance training on stroke volume during incremental exercise (Error Bars = SD). a, significantly different from rest; f, significantly different from all other staged heart rates; *, main effect for weeks six and 12 of training ($p < 0.05$).

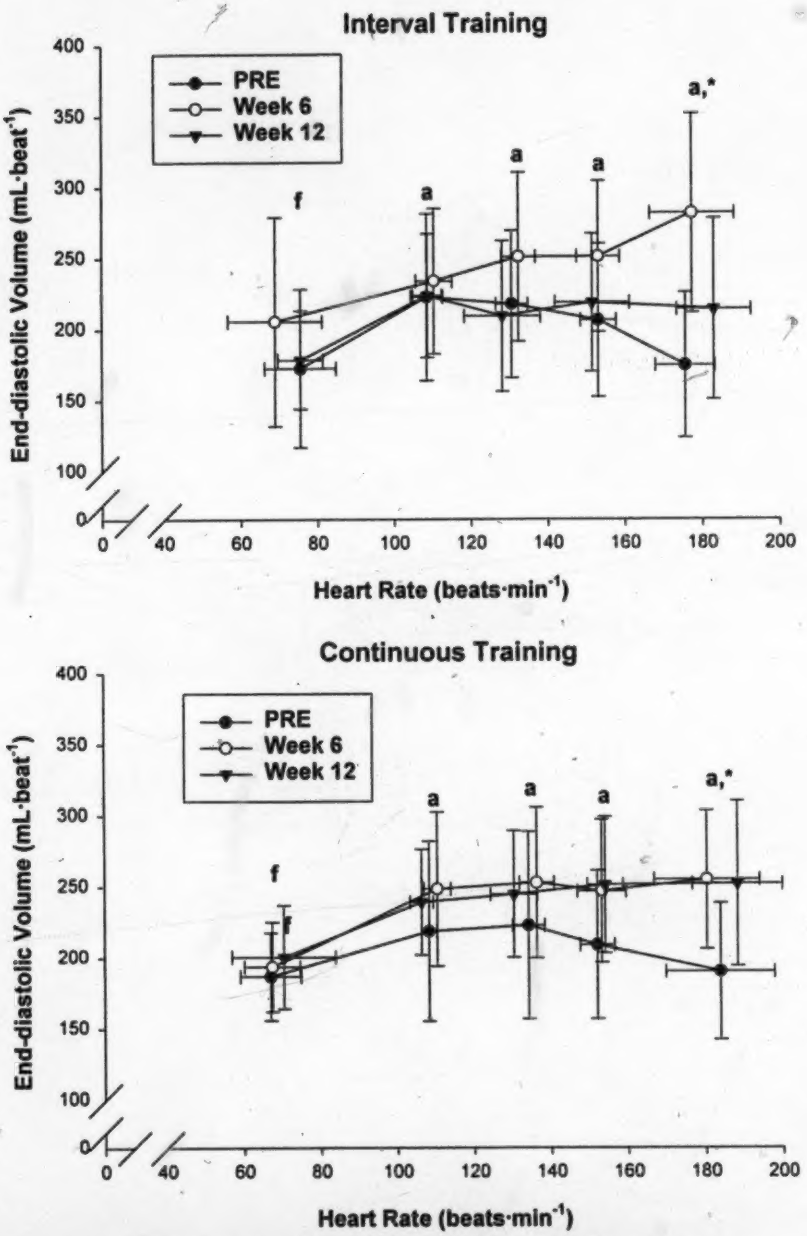
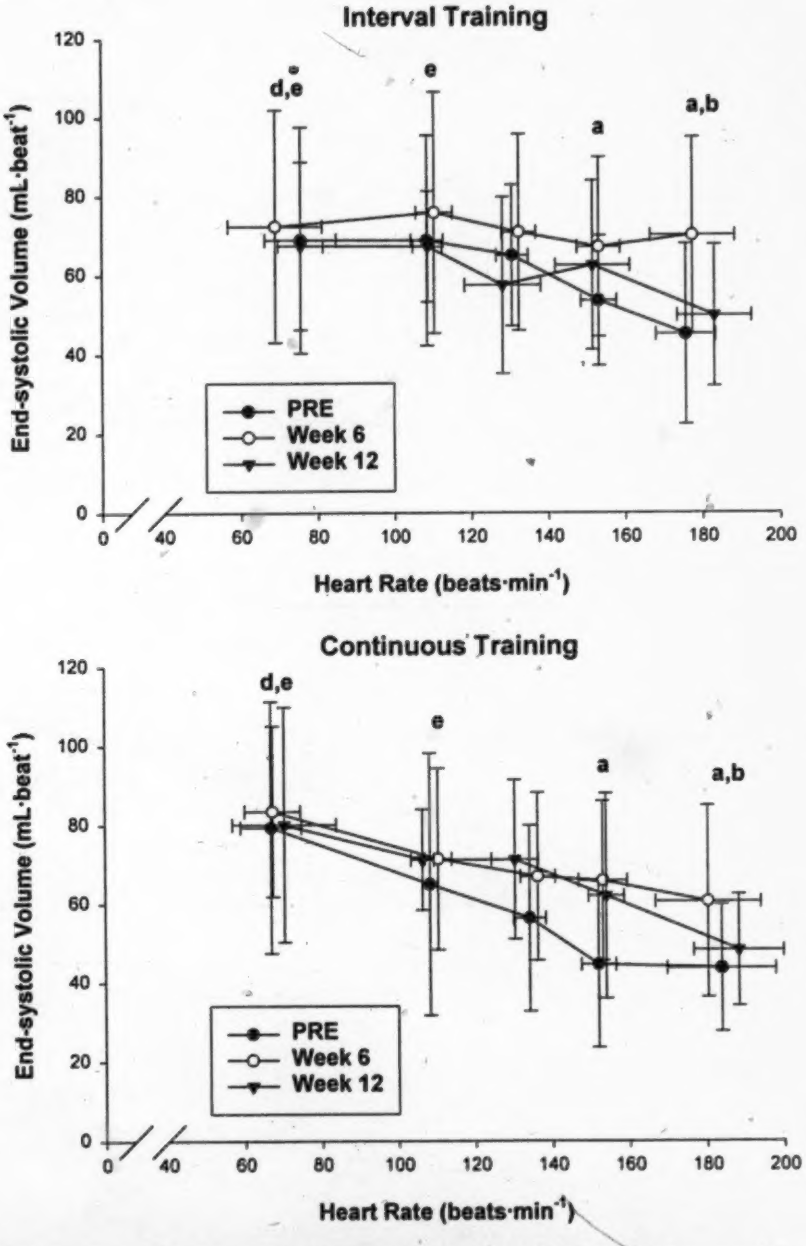


Figure 4.12. Effects of endurance training on end-diastolic volume during incremental exercise (Error Bars = SD). a, significantly different from rest; f, significantly different from all other staged heart rates; *, main effect for weeks six and 12 of training ($p < 0.05$).



Interval Training

Continuous Training

Figure 4.13. Effects of endurance training on end-systolic volume during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats.min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise ($p < 0.05$).

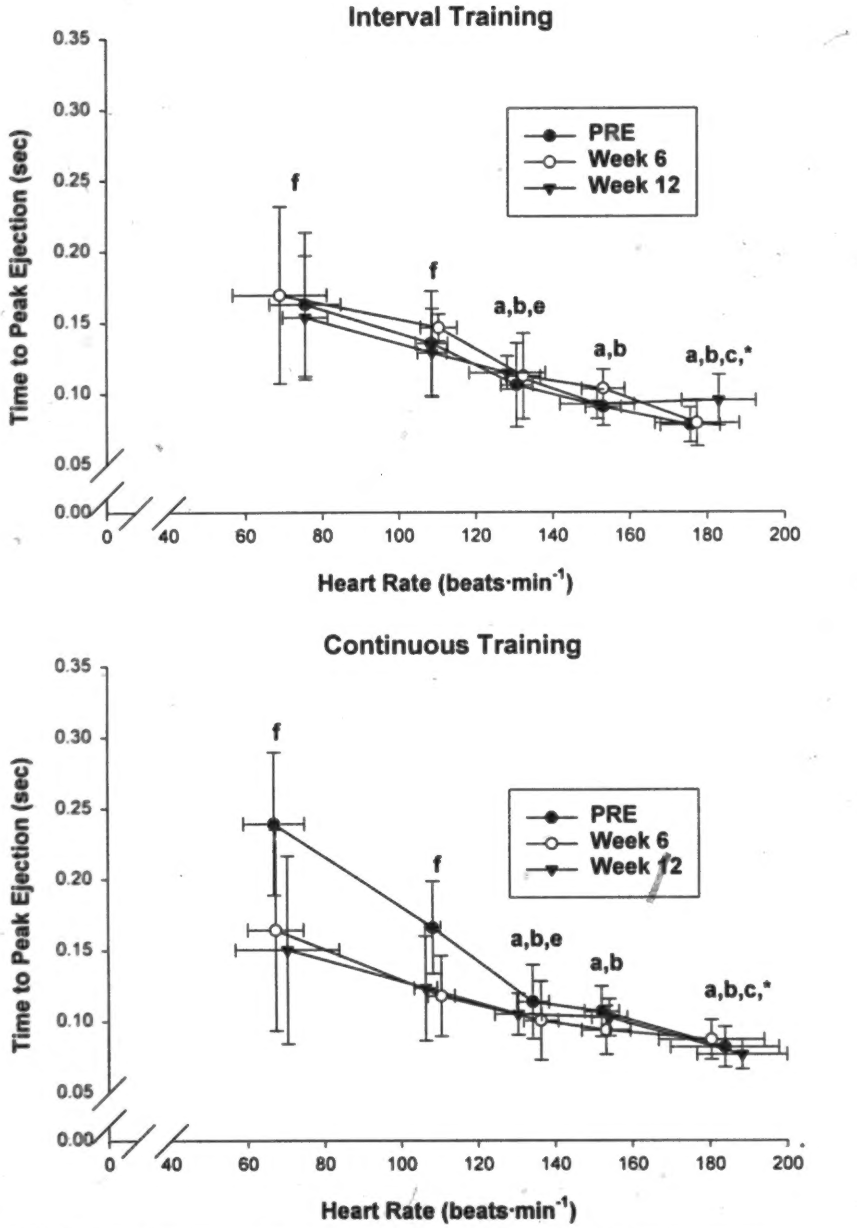


Figure 4.14. Effects of endurance training on time to peak ejection during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates; *, main effect for week 12 of training ($p < 0.05$).

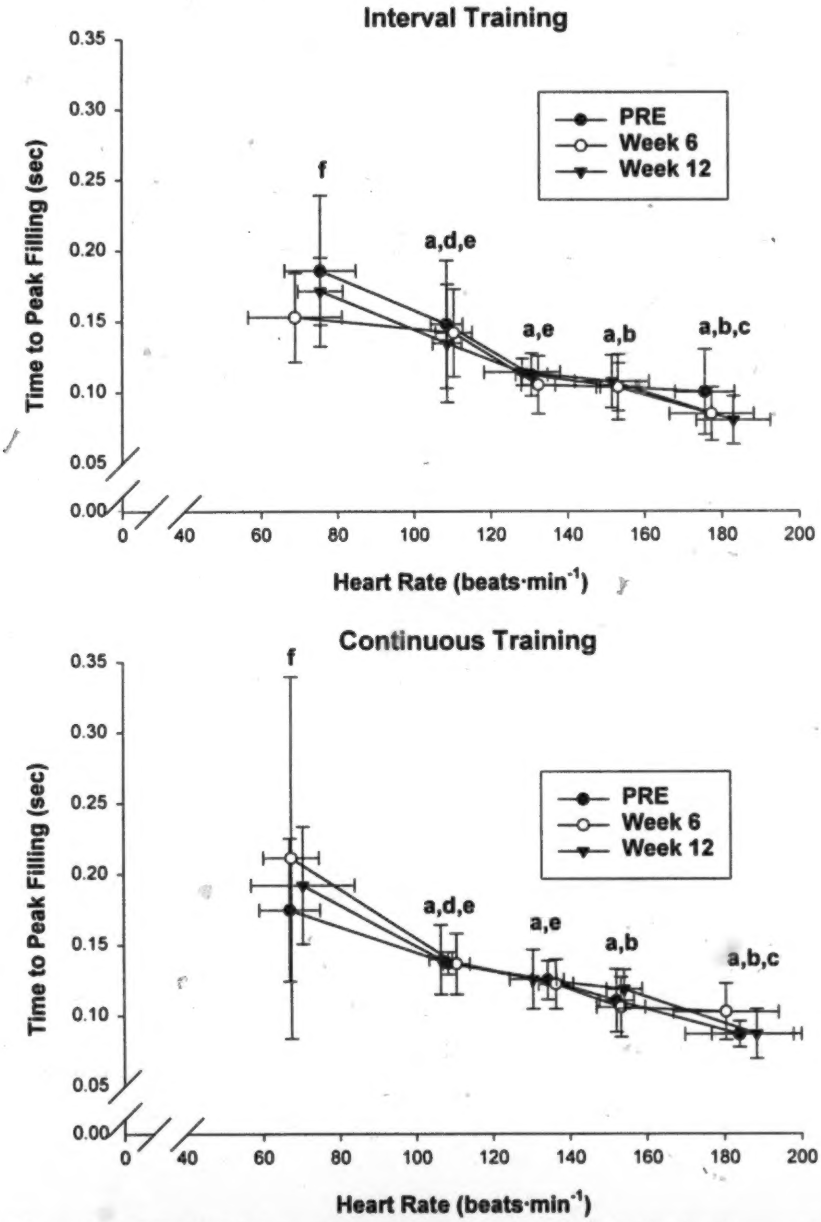
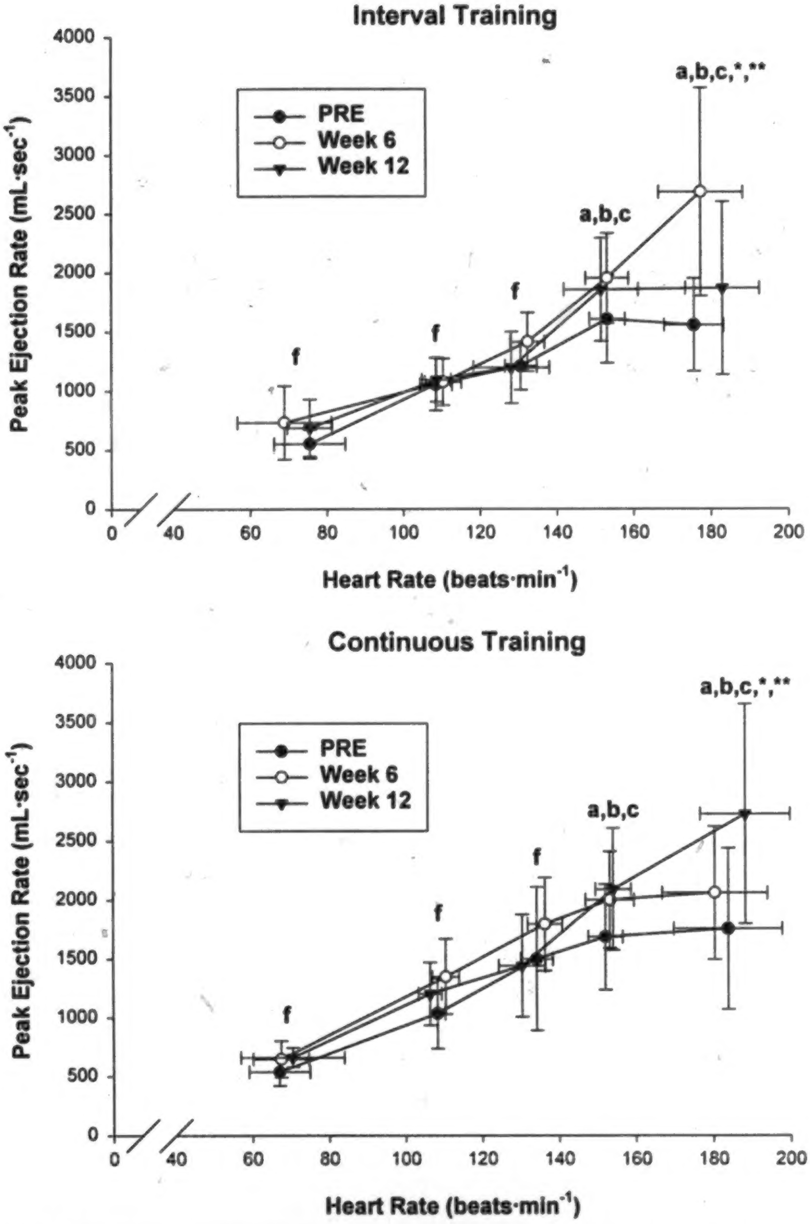


Figure 4.15. Effects of endurance training on time to peak filling during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates ($p < 0.05$).



Interval Training

Continuous Training

Figure 4.16. Effects of endurance training on peak ejection rate during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; f, significantly different from all other staged heart rates; *, main effect for weeks six and 12 of training; **, continuous training greater than interval training ($p < 0.05$).

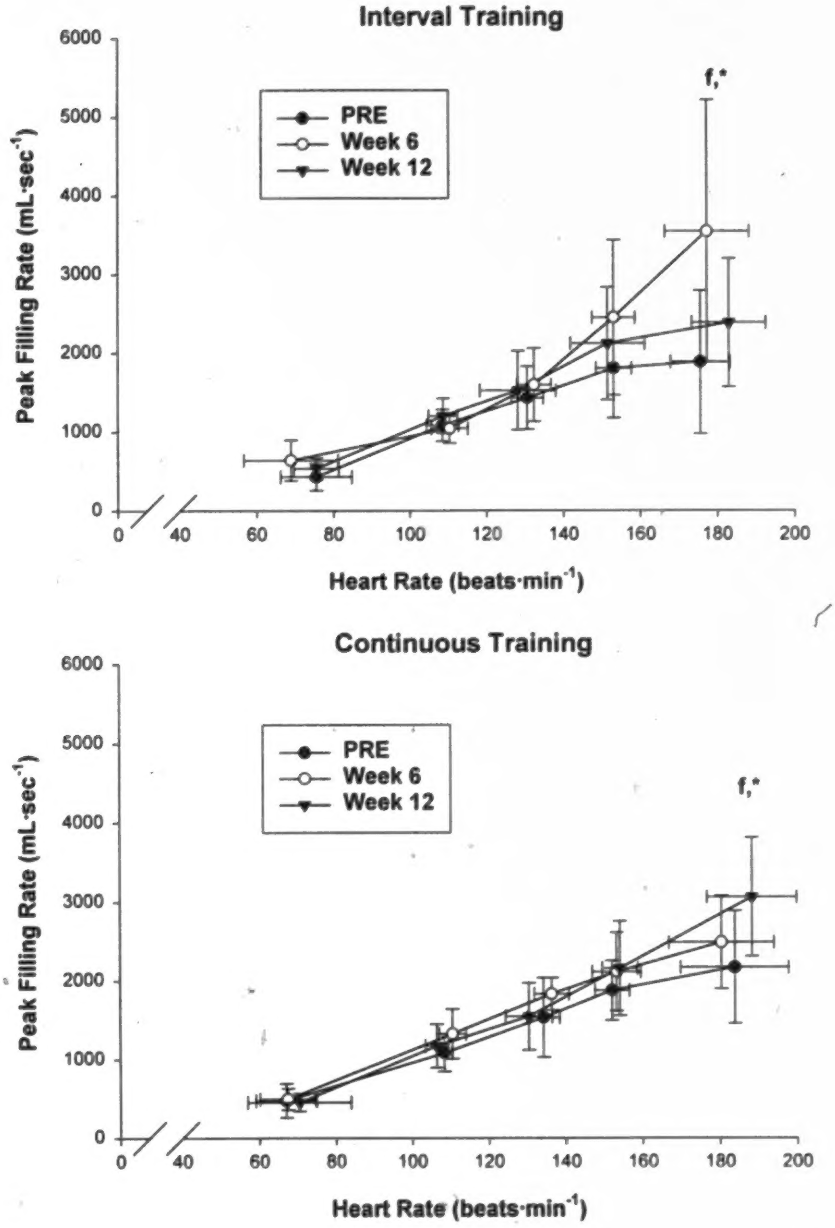


Figure 4.17. Effects of endurance training on peak filling rate during incremental exercise (Error Bars = SD). f, significant difference throughout incremental exercise; *, main effect for weeks six and 12 of training ($p < 0.05$).

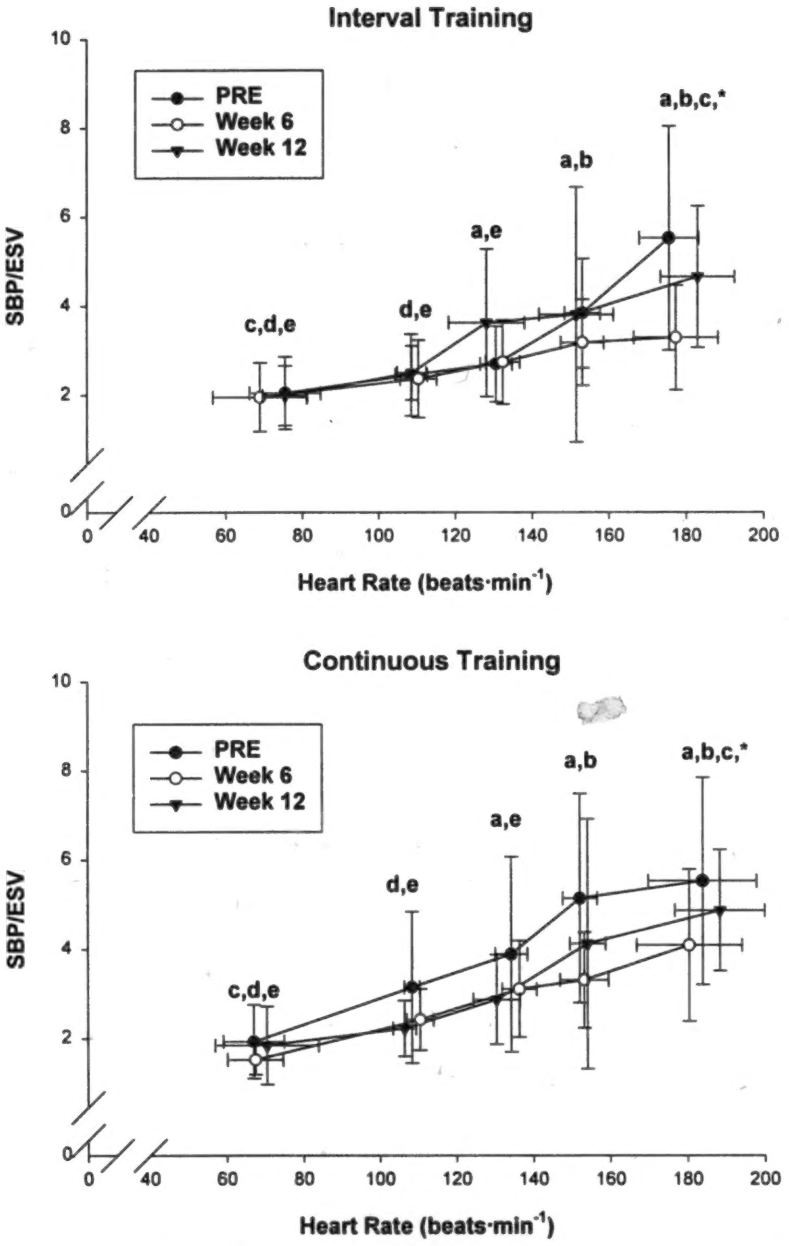


Figure 4.18. Effects of endurance training on the systolic blood pressure to end-systolic volume ratio during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; c, significantly different from 130 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates; *, main effect for week six of training ($p < 0.05$).

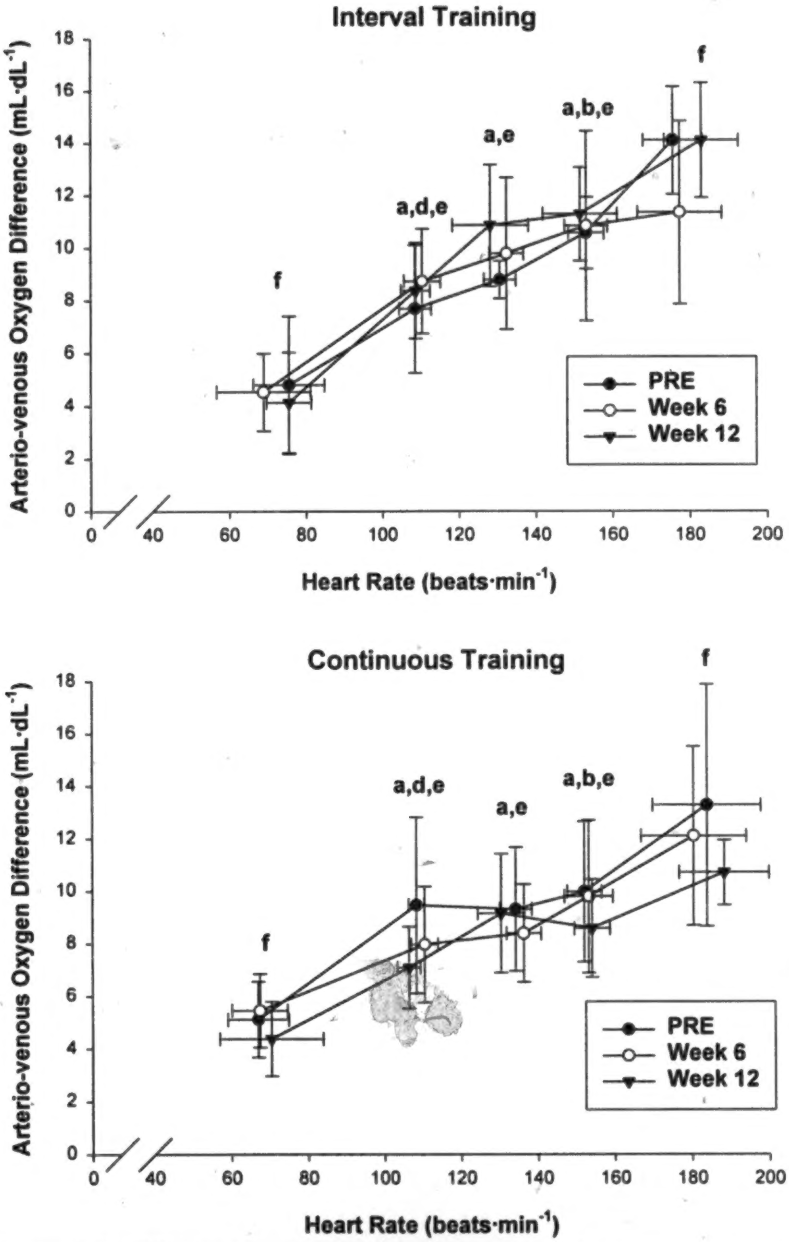


Figure 4.19. Effects of endurance training on arterio-venous oxygen difference during incremental exercise (Error Bars = SD).
a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximal exercise; f, significantly different from all other stages ($p < 0.05$).

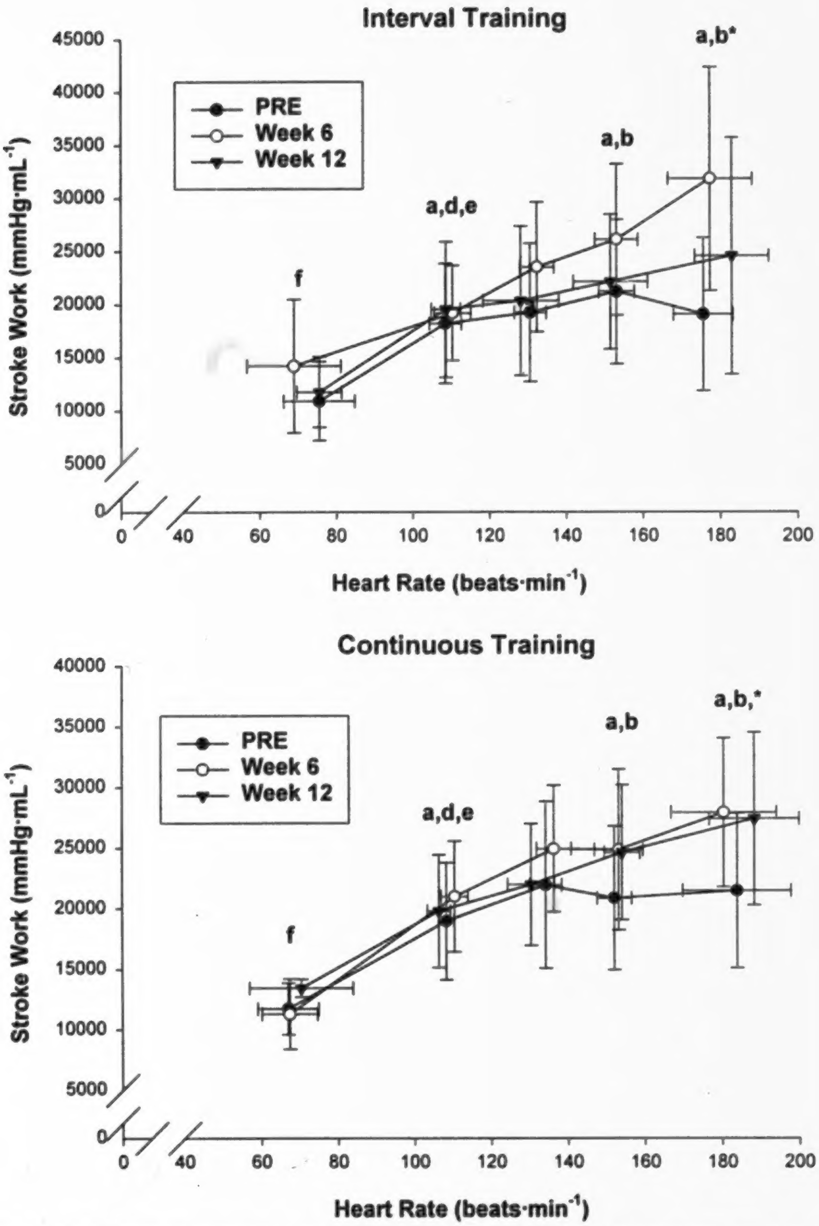
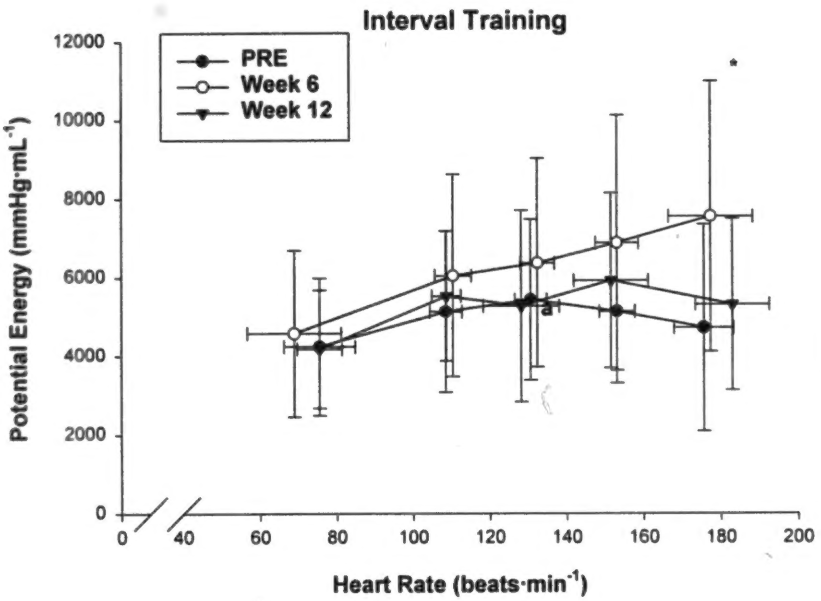


Figure 4.20. Effects of endurance training on stroke work during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; d, significantly different from 150 beats·min^{-1}; e, significantly different from maximum exercise; f, significantly different from all other staged heart rates; *, main effect for week six of training ($p < 0.05$).



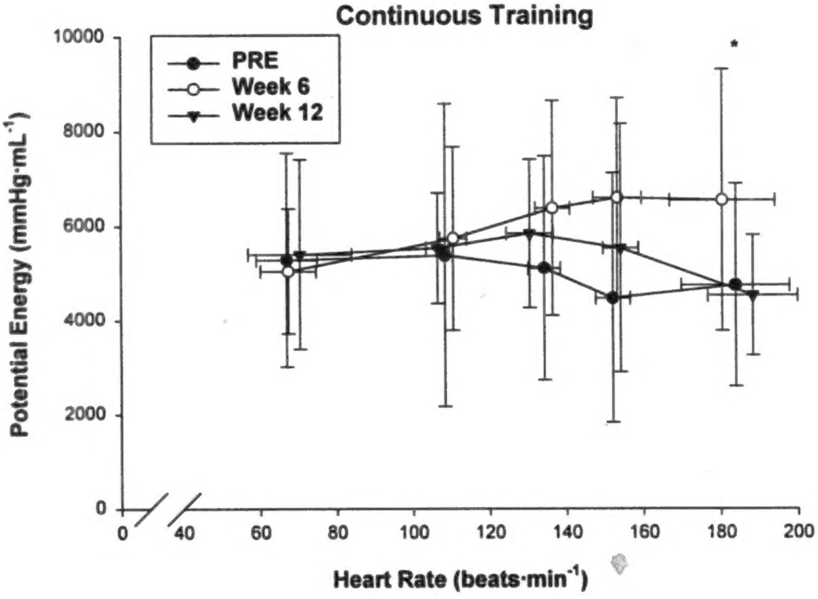


Figure 4.21. Effects of endurance training on potential energy during incremental exercise (Error Bars = SD). *, main effect for week six of training ($p < 0.05$).

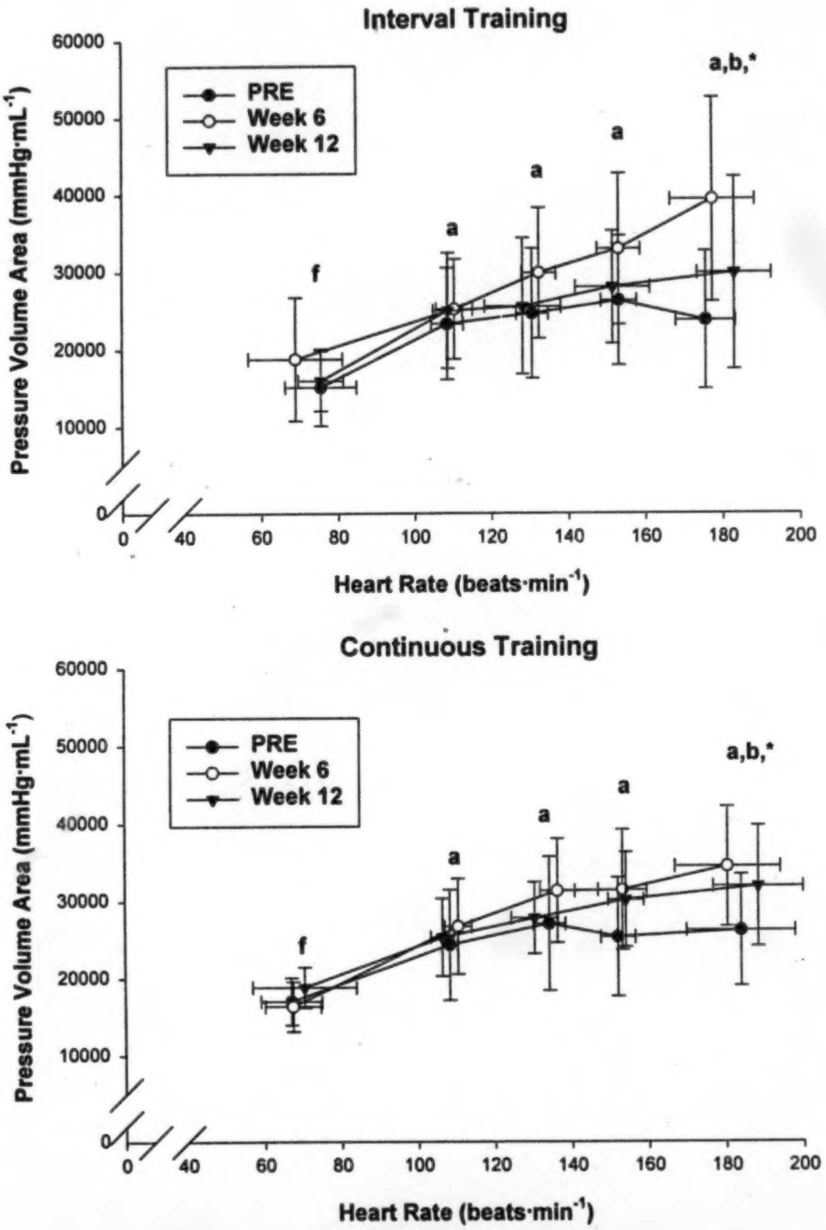


Figure 4.22. Effects of endurance training on pressure-volume area during incremental exercise (Error Bars = SD). a, significantly different from rest; b, significantly different from 110 beats·min^{-1}; f, significantly different from all other staged heart rates; *, main effect for week six of training ($p < 0.05$).

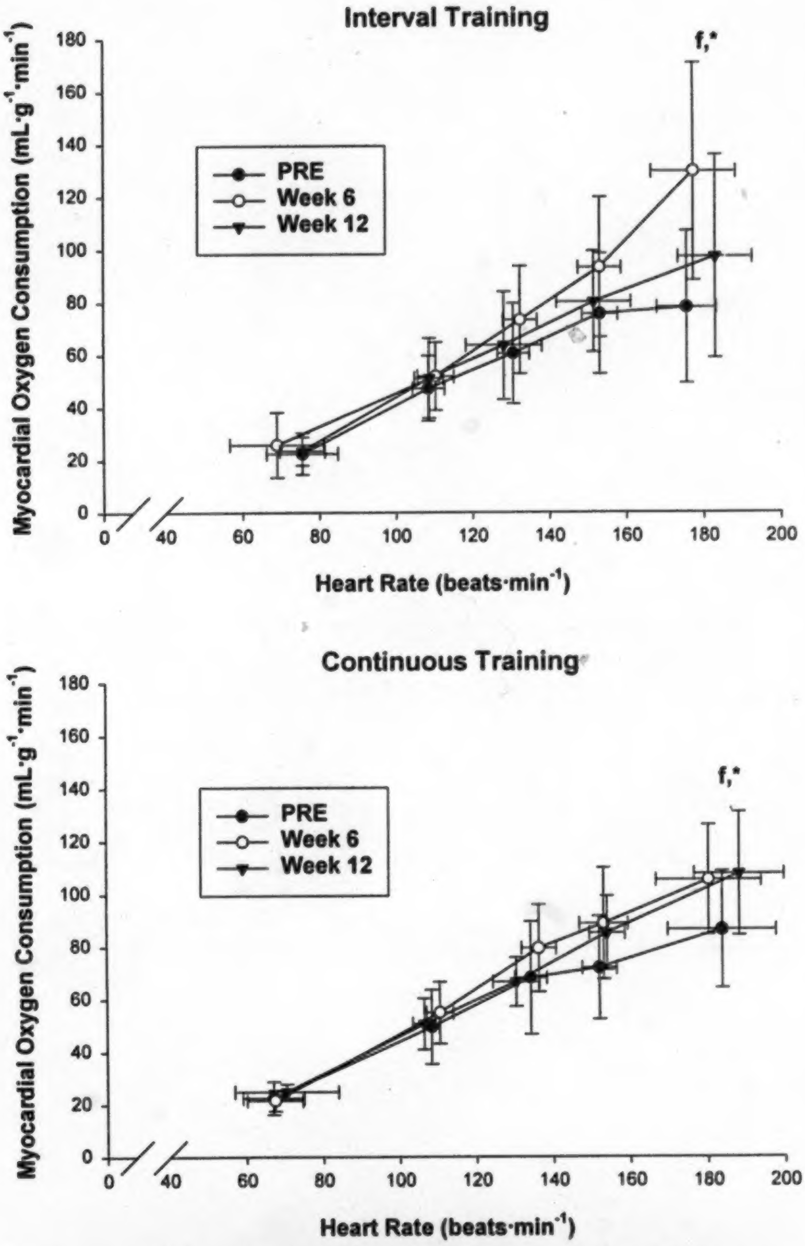
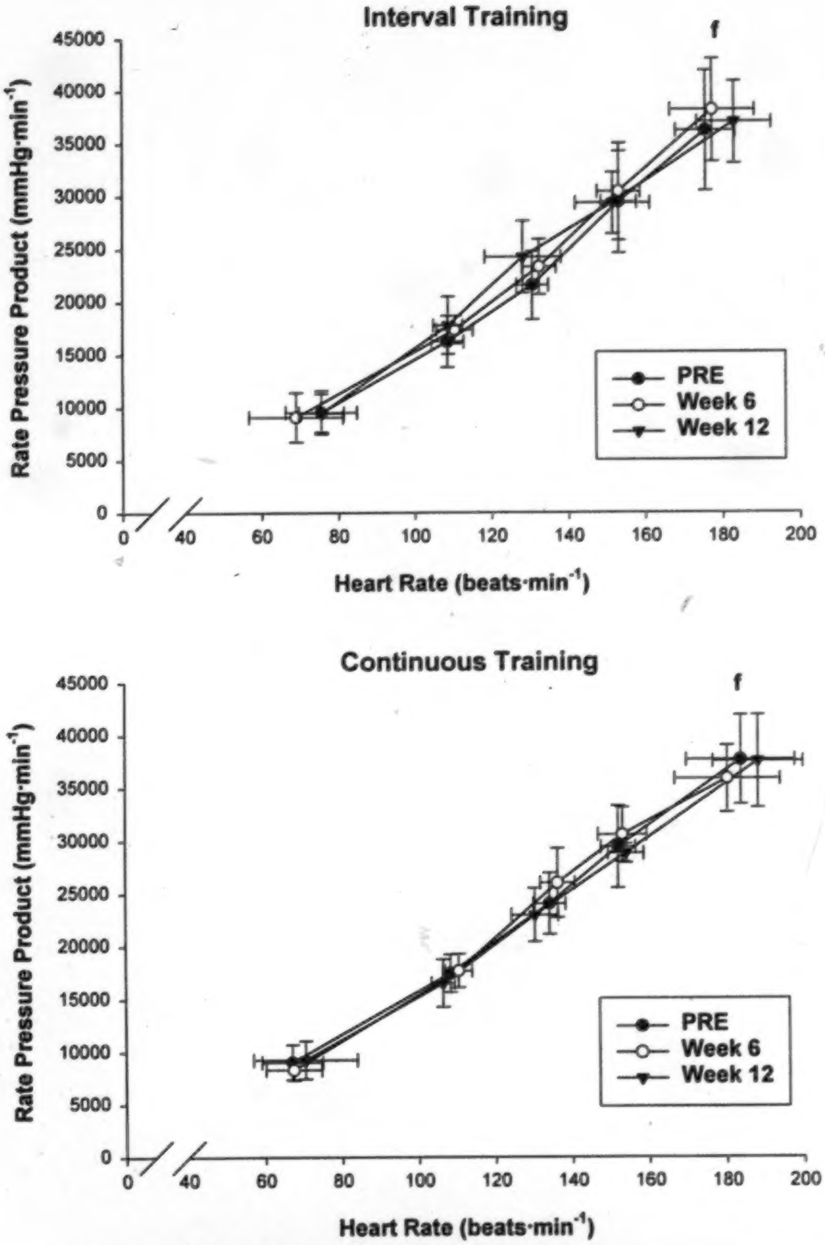


Figure 4.23. Effects of endurance training on myocardial oxygen consumption during incremental exercise (Error Bars = SD). *, main effect for training for week six of training; f, significant difference throughout incremental exercise ($p < 0.05$).



Interval Training

Continuous Training

Figure 4.24. Effects of endurance training on rate-pressure product during incremental exercise (Error Bars = SD). f, significant difference throughout incremental exercise ($p < 0.05$).

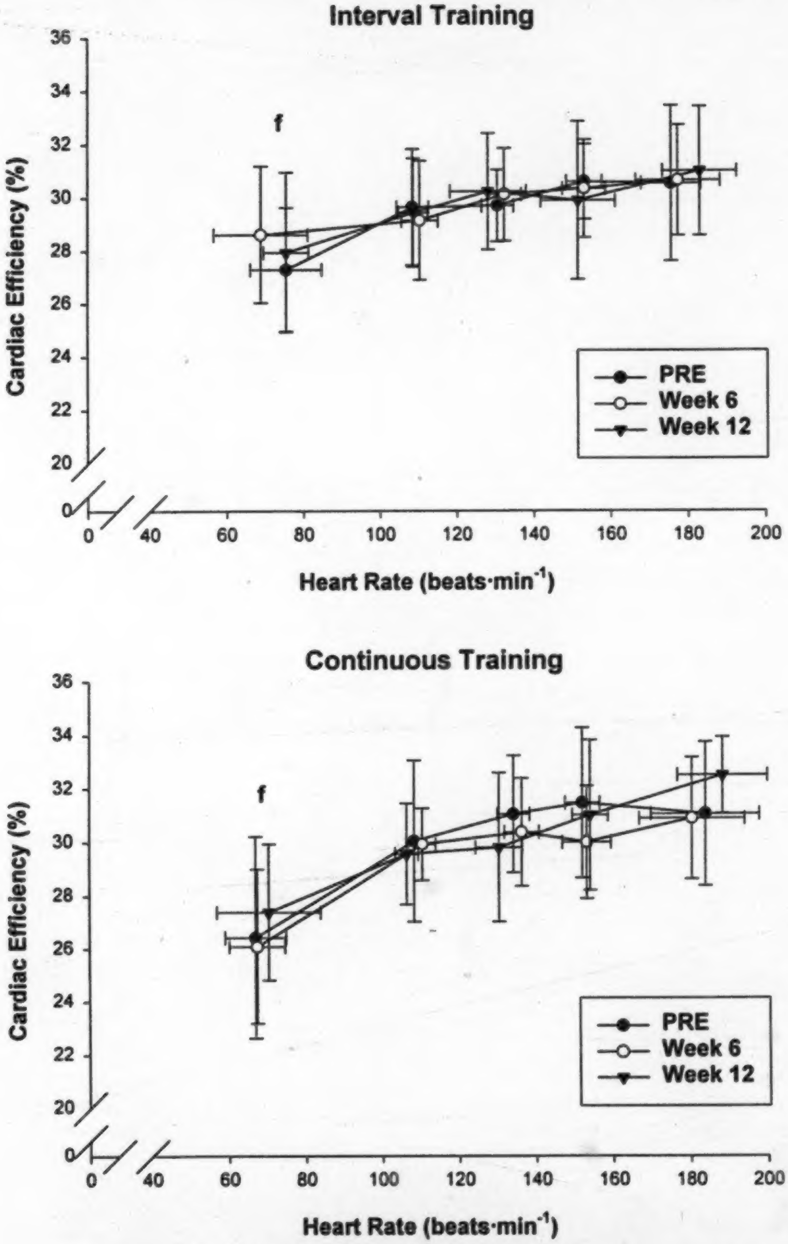


Figure 4.25. Effects of endurance training on myocardial efficiency during incremental exercise (Error Bars = SD). f, significantly different from all other staged heart rates ($p < 0.05$).

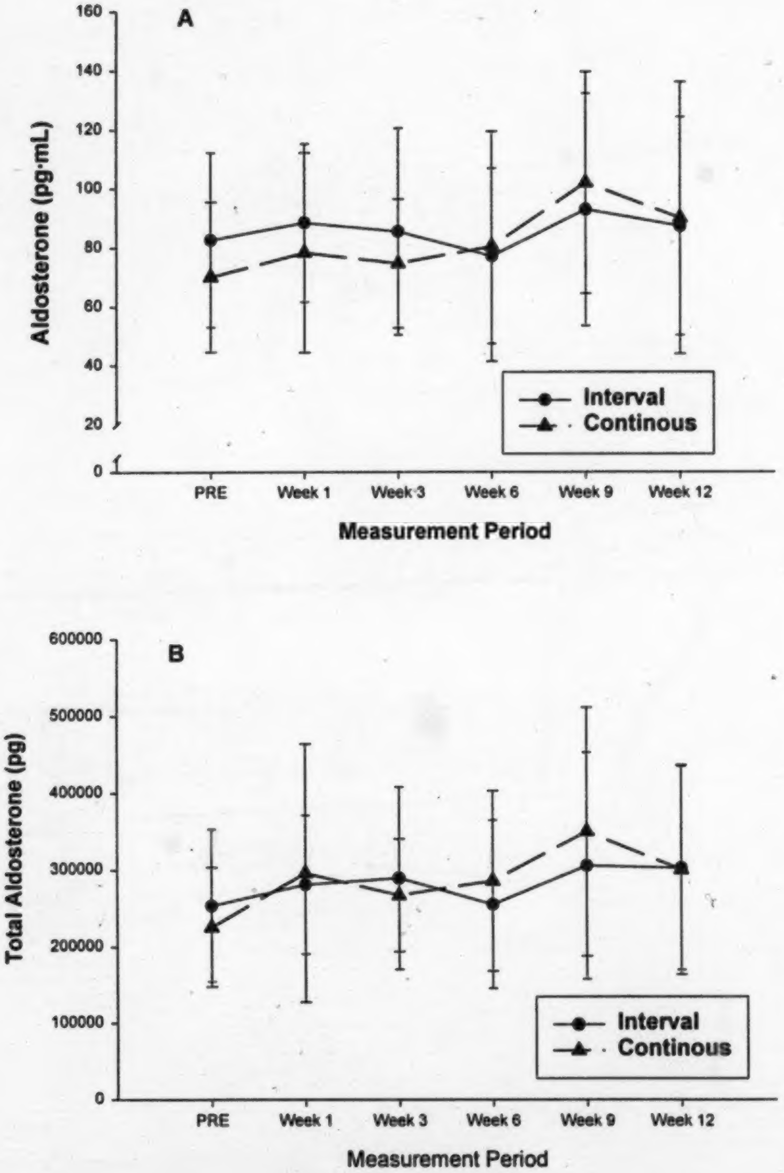


Figure 4.26. Effects of endurance training on serum aldosterone concentration (A) and total aldosterone (B) (Error Bars = SD).

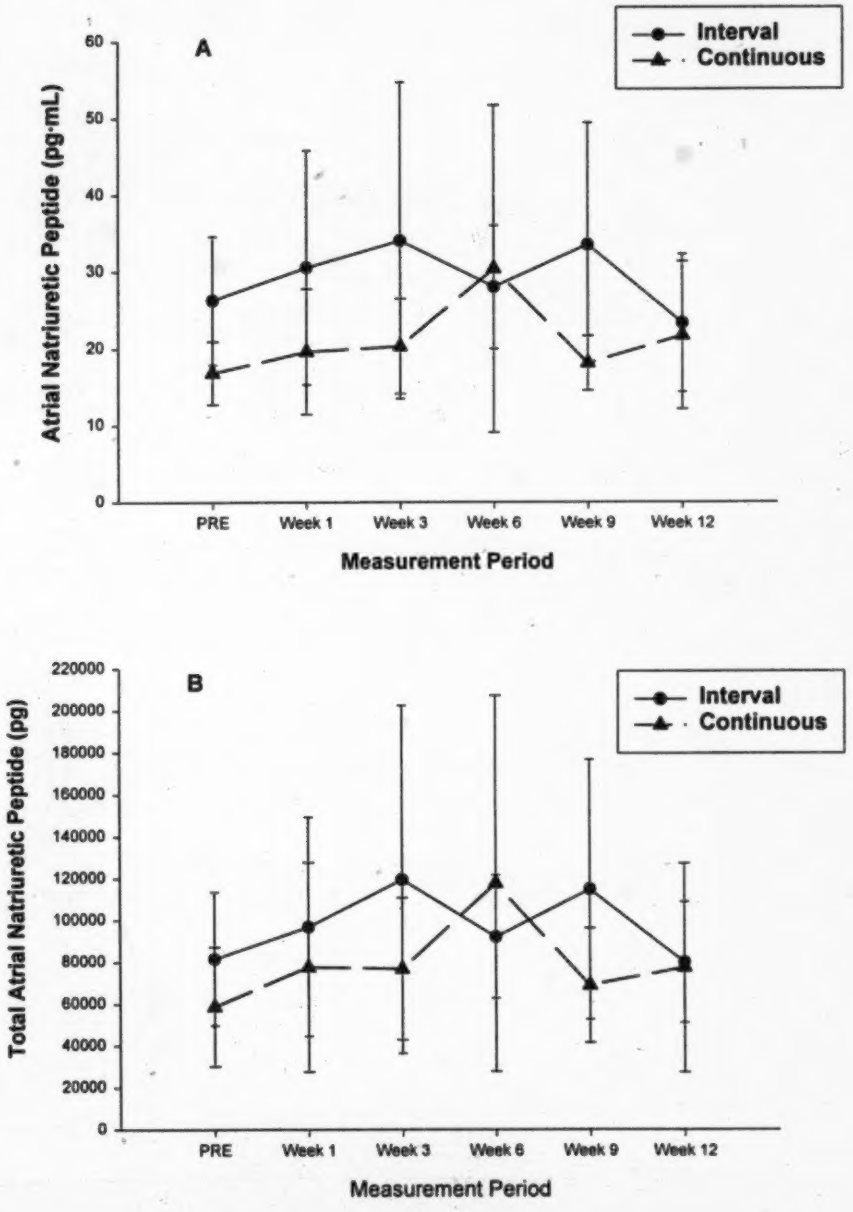


Figure 4.27. Effects of endurance training on plasma atrial natriuretic peptide concentration (A) and total atrial natriuretic peptide (B) (Error Bars = SD).

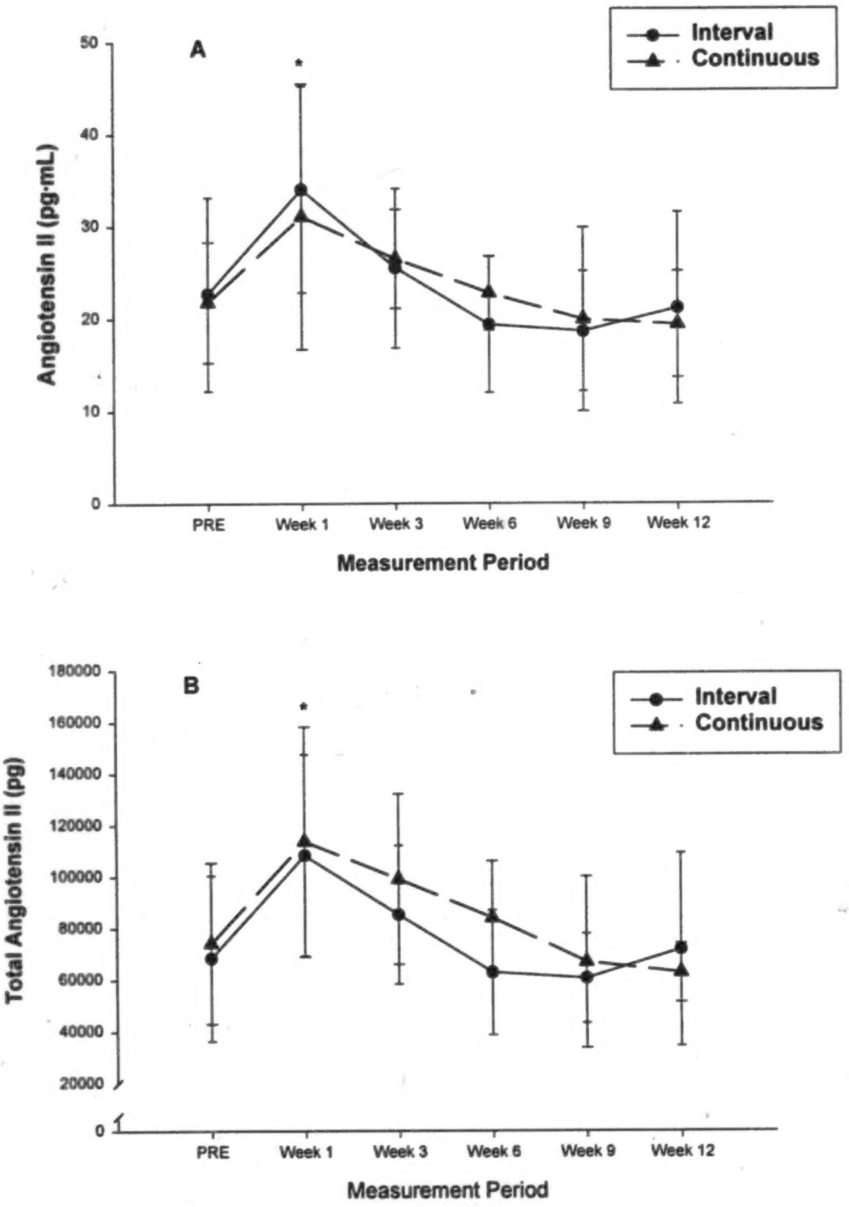


Figure 4.28. Effects of endurance training on plasma angiotensin II concentration (A) and total angiotensin II (B) (Error Bars = SD). *, significantly different from PRE, and weeks six, nine, and 12 ($p < 0.05$).

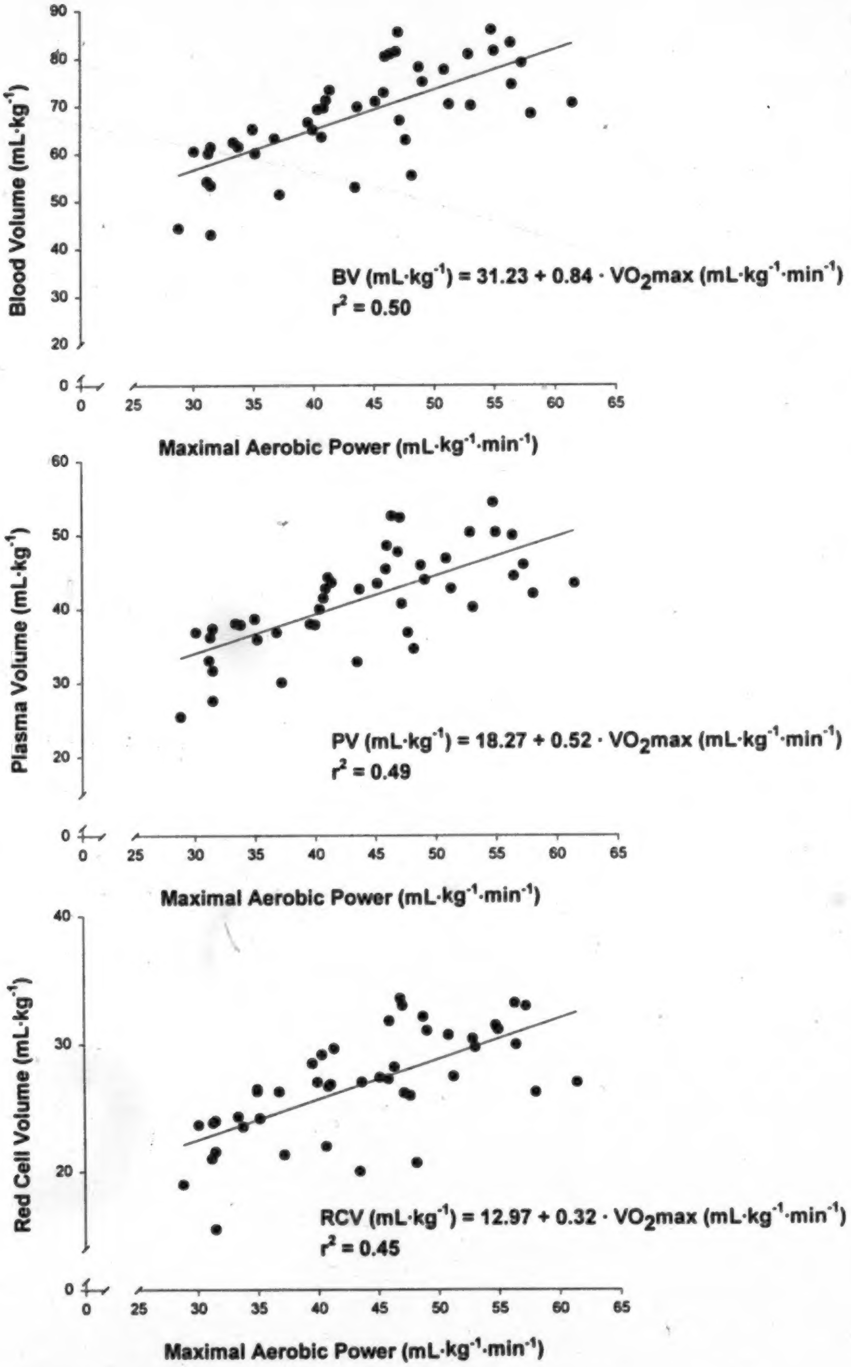


Figure 4.29. Relationships between vascular volumes and maximal aerobic power as a result of endurance training.

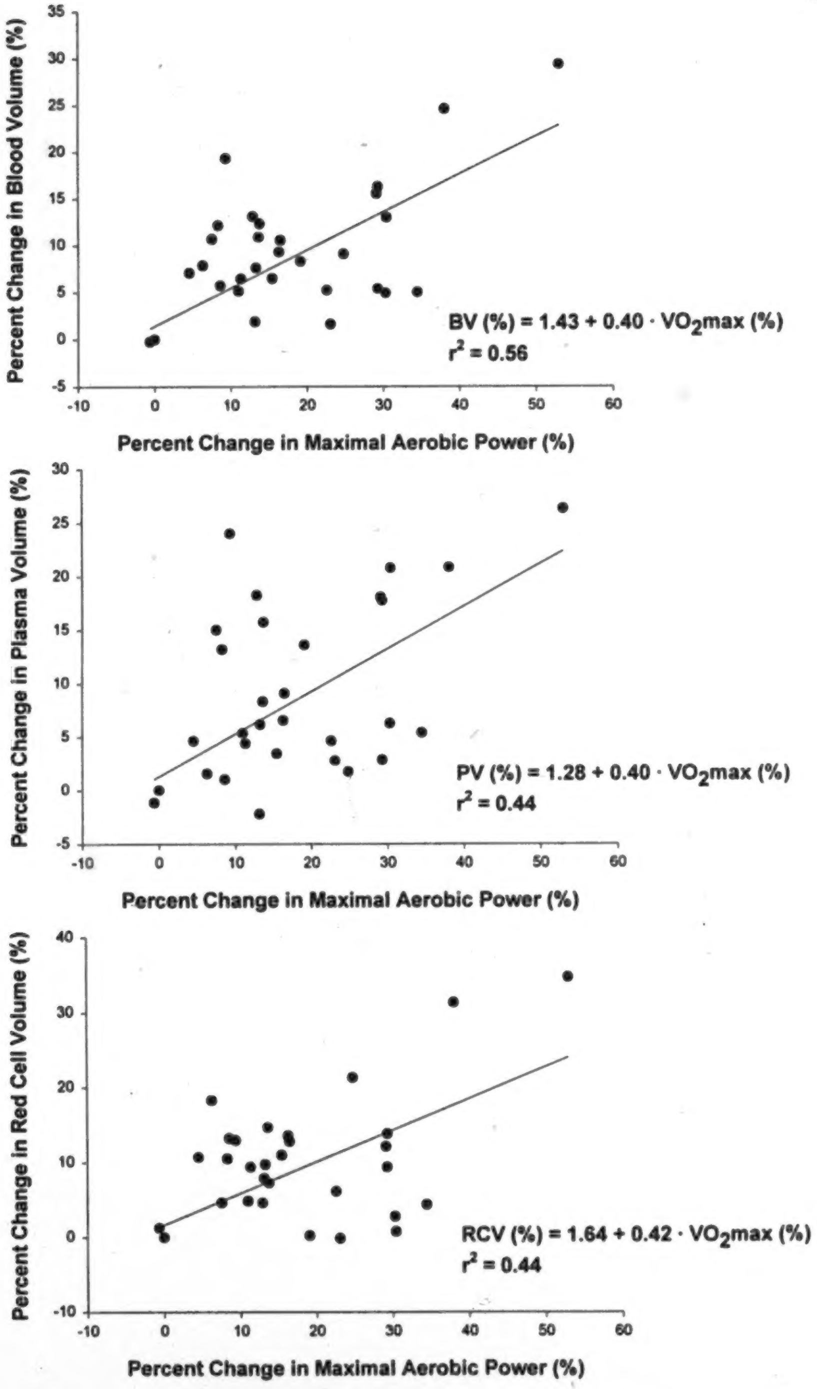


Figure 4.30. Relationships between percent changes in vascular volumes and percent changes in maximal aerobic power as a result of endurance training.

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CHAPTER FIVE

Haematological and Biochemical Response to the Half Ironman Triathlon

ABSTRACT

Purpose: The objective of this investigation was to evaluate the haematological and biochemical response to the Half Ironman Triathlon (Swim = 2 km, Bike = 90 km, Run = 21 km). Methods: Blood samples were taken in nine male triathletes (mean age ± SD = 32 ± 5 years) 48-72 hr before (PRE), 15-30 min after (POST), and 24-48 hr after (RECOVERY) the Half Ironman Triathlon. Results: Plasma concentrations of sodium, potassium, and magnesium were not significantly affected. Significant increases were observed POST in white blood cell count (168.1%), platelet count (11.2%), and creatinine (17.5%) and urea (19.0%) concentration. Chloride concentration was significantly reduced (6.7%) POST. Significant reductions were observed after RECOVERY in haemoglobin concentration (8.1%), haematocrit (9.1%), and red blood cell (RBC) count (8.3%). Conclusions: Reductions in haemoglobin concentration and haematocrit occur after Half Ironman Triathlon participation, in part due to a reduction in RBC. Competition in the Half Ironman Triathlon does not result in significant hyponatremia, hypokalemia or hypomagnesia.

INTRODUCTION

Athletes engaged in prolonged strenuous exercise training commonly exhibit a sub-optimal haemoglobin concentration ([Hb]) and haematocrit (Hct) level, without any medical explanation (4, 9). This condition is referred to as "sports anaemia" and generally represents a dilutional anaemia, which probably has little impact on sports performance (4, 41, 42). However, sports anaemia may also be due to; 1) a blunted erythropoeitic drive due to improved tissue oxygenation, 2) foot strike destruction of red blood cells (haemolytic anaemia) and/or 3) loss of iron through sweat/urine and gastrointestinal (GI) blood loss (iron deficiency) (13, 22, 33).

Small reductions in red blood cells (RBC) have been shown to have a significant impact on maximal oxygen consumption ($\dot{V}O_2$max) and endurance performance (7, 16). Gledhill and coworkers (10) approximated that a small reduction in [Hb] as a result of RBC removal of 30 $g \cdot L^{-1}$ will result in an approximate reduction in $\dot{V}O_2$max of 1% and a 2% impairment of endurance performance. From a performance standpoint it is important to understand what effects various forms of exercise have on [Hb] and RBC.

The Triathlon has recently gained widespread popularity, however, a paucity of information exists regarding the effects of this form exercise on Hb, RBC and a series of other haematological measures (Hct, white blood cell count (WBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), platelet count, RBC distribution of widths (RDW)).

It is also apparent that prolonged strenuous exercise may result in significant biochemical alterations. Low plasma or serum concentrations of sodium (Na^+) (hyponatremia), (14, 26, 27), potassium (K^+) (hypokalemia) (21) and/or magnesium (Mg^{2+}) (hypomagnesia) (8, 20, 36) have been reported after prolonged endurance exercise. These alterations may have serious implications from both a health- and performance-related point of view. However, a paucity of information exists regarding the effects of a Half Ironman Triathlon on these biochemical parameters.

Therefore, the primary purpose of this investigation was to evaluate the effects of prolonged strenuous exercise, in the form of the Half Ironman Triathlon, on a wide range of haematological and biochemical parameters. It is hoped that this knowledge will help establish the effects of ultra endurance events on haematological and biochemical blood parameters, which may be used in the understanding of the upper limits of human performance.

METHODS

Participants

Nine male triathletes, ranging in age from 23 to 38 years (mean ± SD = 32 ± 5 years) volunteered for this investigation with informed consent and approval of the human research ethics committee. Baseline clinical characteristics of the subjects are summarized in Table 5.1. Participants were selected for this investigation based on the entrance criteria of a predicted completion time of five hours or less. Exclusion criteria for these athletes included the following: 1) any known myocardial disease, 2) presence of risk factors for coronary artery disease, 3) family history of sudden cardiac death at a young age, and 4) uninterpretable ECG, such as bundle branch block. Subjects participated in regimented training programs in preparation for triathlon competitions training on average 12 hours per week (Table 5.2). The participants were entered in a standard Half Ironman Triathlon, with a 2 km swim, a 90 km bike and a 21 km run.

Blood Sampling

Venous blood samples were taken from an antecubital vein 48-72 hr before (PRE), 15-30 min after (POST), and 24-48 hr after (RECOVERY) the completion of a Half Ironman Triathlon. All samples were assayed in duplicate and the mean of the duplicates was reported. The cutoff coefficient of variation for duplicate measures was > 15%.

Haematologic Measures

Blood samples for the haematologic procedures were collected into chilled sterile vacutainer tubes (3 ml) containing EDTA as an anti-coagulant and stored at room temperature until analysis. Haematologic measures – [Hb], Hct, RBC, WBC, MCV, MCHC, and platelet count – were determined using standard techniques on a Coulter Stack S (STKS). The expression of the coefficient of variation of RBC volume of distribution (RDW) was also calculated. Haematocrit was determined from the relative volume of RBCs in whole blood using the Coulter method of counting and sizing (Appendix E). Mean corpuscular volume can be directly read from the red cell volume histogram given by the Coulter counter or determined by the following equation:

$$\mathrm{MCV} = {}^{\mathrm{Hct}}\!/_{\mathrm{RBC}}$$

Mean corpuscular haemoglobin was determined via the following equation:

$$\mathrm{MCH} = {}^{\mathrm{Hb}}\!/_{\mathrm{RBC}}$$

Mean corpuscular haemoglobin concentration was according to the following equation:

$$\mathrm{MCHC} = {}^{\mathrm{Hb}}\!/_{(\mathrm{RBC} \bullet \mathrm{MCV})}$$

Biochemical Measures

Blood samples for the biochemical analyses were collected into chilled sterile vacutainer tubes (3 ml) containing lithium heparin as an anti-coagulant and stored at room temperature until analysis. Blood samples were spun at 4,000 $\mathrm{revs \cdot min^{-1}}$ for 10 min at 4°C. All blood analyses were conducted at the University of Alberta Hospital by trained personnel from the Department of Laboratory Medicine and Pathology.

Plasma Magnesium

Plasma concentrations of Mg^{2+} were measured using standard laboratory procedures on a Hitachi 917 analyser. Magnesium ions form a colour complex (purple-red) with xylidyl blue I in alkaline solution. The Mg^{2+} concentration in 4 μL of heparinized plasma is measured by a decrease in absorbency at 600 nm on a Hitachi 917 analyser.

Plasma Sodium, Potassium and Chloride

Plasma concentrations of Na^+, K^+, and Cl^- (in 15 μl of heparinized plasma) were measured using ion-specific electrodes on a Hitachi 917 chemical analyser. The ion-specific electrodes consist of a Na^+ electrode, a K^+ electrode and a Cl^- sensitive electrode. All samples were diluted 1:31 before passing through the electrodes. The change in electromotive force (EMF) measured in the circuit between the reference electrode and the ion-specific electrode was converted to concentrations using the following equation:

$$\text{EMF (millivolts)} = \pm\ 61 \log \frac{C_1}{C_2}$$

where EMF is the electromotive force (voltage) between side 1 and side 2 of the membrane, C_1 is the concentration on side 1, and C_2 is the concentration on side 2. The within run coefficient of variation for the measurement of Na^+, K^+, and Cl^- is approximately 1%. The total coefficient of variation for the measurement of Na^+, K^+, and Cl^- is 1 to 2%.

Plasma Bicarbonate

Plasma HCO_3^- was determined using the kinetic UV Boehringer Mannheim assay on a Hitachi 917 analyser. The HCO_3^- procedure is a two-point reaction in which HCO_3^- reacts with phosphoenolpyruvate (PEP) in the presence of phosphoenolpyruvate carboxylase (PEP-C) to produce oxaloacetate and phosphate:

$$\text{PEP} + HCO_3^- \xrightarrow{PEP-C} \text{oxaloacetate} + H_2PO_4$$

Oxaloacetate is then converted to malate by malate dehydrogenase (MDH) with the subsequent oxidation of NADH:

$$\text{oxaloacetate} + \text{NADH} \xrightarrow{\text{MDH}} \text{NAD}^+ + \text{malate}$$

The resultant disappearance of NADH results in a decrease in the absorbance in the UV range, which is directly proportional to the concentration of HCO_3^- in the sample of 2.5 µl of heparinized plasma (measured at 376 nm on a Hitachi 917 analyser).

Plasma Urea

Plasma urea concentration was determined using the kinetic (fixed-time) UV Boehringer Mannheim urea/BUN assay on a Hitachi 917 analyser. Urea is hydrolysed by urease to form carbon dioxide (CO_2) and ammonia (NH_4^+):

$$\text{Urea} + H_2O \xrightarrow{\text{Urease}} 2\,NH_4^+ + CO_2$$

The indicator reaction combines NH_4^+ with α-oxoglutarate and NADH in the presence of glutamate dehydrogenase (GLDH) to produce glutamate and NAD$^+$:

$$\alpha - \text{ketoglutarate} + NH_4 + NADH \xrightarrow{\text{GLDH}}$$
$$\text{L-glutamate} + NAD + H_2O$$

The decrease in absorbance due to the consumption of NADH is measured at 340 nm in a sample of 3 μl of heparinized plasma.

Plasma Creatinine

Creatinine concentration in 2.5 μl of heparinized plasma was determined using the Roche Creatinine Jaffé method (i.e., a kinetic colorimetric assay) on a Hitachi 917 analyser. In an alkaline solution, creatinine forms a coloured (yellow-orange) complex with picrate:

$$\text{creatinine} + \text{picric acid} \xrightarrow[\text{solution}]{\text{alkaline}} \text{creatinine - picric acid complex}$$

The colour intensity of this reaction is directly proportional to the creatinine concentration and can be measured photometrically at 505 nm. The anion gap (AG) was calculated as $[(Na^+ + K^+) - (HCO_3^- + Cl^-)]$ to aid in the diagnosis of metabolic acidosis.

Plasma Catecholamines

Blood samples for the measurement of plasma catecholamines were collected into two 5 ml vacutainer tubes (pre-cooled) containing EDTA as an anti-coagulant. Samples were immediately placed on ice and processed within a half hour of collection. Blood samples were spun at 4,000 revs·min^{-1} for 10 min at 4°C. The plasma was then transferred (a minimum of 2.5 ml) into two separate plastic vials and stored immediately at -20°C until analysis. Catecholamines were analysed using standard high pressure liquid chromatography (HPLC) procedures at Foothills Hospital, Calgary, Alberta.

STATISTICS

Alterations in the haematologic and biochemical parameters of interest were evaluated using appropriate repeated measures analysis of variance. Tukey *post hoc* comparisons were used to identify differences between means when main effects were observed. The level of significance was set a priori at $p < 0.05$. The relationship between endogenous catecholamine and serum electrolyte levels was determined via linear regression.

RESULTS

The mean values (± SD) and the statistical significance for all measurements during PRE, POST, and RECOVERY conditions are reported in Tables 5.2 and 5.3. For the sake of clarity, each parameter is discussed separately.

Haemoglobin, Red Blood Cells and Haematocrit

In comparison to PRE, there were no significant changes in Hb, RBC or Hct in the samples taken POST (Table 5.3). A significant reduction in Hb (8.1%), RBC (8.3%) and Hct (9.1%) was observed during RECOVERY. During baseline conditions, none of the participants displayed mild anaemia ([Hb] < 140 g/L), or RBC and Hct levels below their respective normal clinical range (Table 5.2). Immediately after the race, one participant displayed a [Hb] and RBC count below the clinical norm (137 g/L and 4.48 x 10^{12}/L, respectively). Two other athletes displayed a below normal RBC value (4.48 x 10^{12}/L, respectively) with a normal [Hb] and Hct during POST. The customary haemoconcentration (i.e., 8 to 10% increase in Hct and [Hb]) observed after prolonged exercise (40) was not observed in any of the triathletes immediately after the race. After RECOVERY, five of the nine participants displayed mild anaemia with a RBC count below the normal range (only two of these athletes displayed a below normal Hct).

Mean Corpuscular Volume, Mean Corpuscular Haemoglobin Concentration, Mean Corpuscular Haemoglobin, and Red Blood Cell Distribution

Mean values for MCV, MCHC, MCH and RDW were all within the normal range before the race (Table 5.2) and remained near baseline levels during POST and RECOVERY. None of the athletes displayed abnormal MCV, MCHC, MCH or RDW during PRE, POST or RECOVERY.

White Blood Cells and Platelet Count

The total WBC count increased significantly (168.1%) after the race. The total WBC count returned to baseline values within 24-48 hrs of recovery (Table 5.2) All nine athletes displayed a WBC concentration above the normal range during POST. No athletes displayed abnormal WBC levels during PRE or RECOVERY.

Competition in the Half Ironman Triathlon resulted in a mean increase in the venous platelet count of 11.2% ($p < 0.05$), which was normalized 48-72 hr after the race. One participant displayed a platelet count ($138 \times 10^9/L$) below the normal range (i.e. mild thrombocytopenia; platelet count $< 150 \times 10^9/L$) during PRE, but none displayed severe thrombocytopenia (platelet count $< 100 \times 10^9/L$). None of the athletes displayed platelet levels beyond the normal range during POST and one athlete displayed mild thrombocytopenia ($141 \times 10^9/L$) after RECOVERY.

Ionic Balance

Cations

There was no significant change in [Na^+], and none of the athletes displayed a [Na^+] beyond the normal range during any of the measurement periods (Table 5.3). Potassium concentration was not significantly altered by competition, despite a 19.5 and 12.2% reduction during POST and RECOVERY, respectively. Two athletes had abnormal K^+ levels (3.3 and 5.8 mmol/L) during PRE, four athletes had below normal K^+ levels (3.2, 3.2, 2.8, and 3.2 mmol/L) during POST, and one subject had abnormal K^+ levels (3.3 mmol/L) during RECOVERY. There was a slight reduction in Mg^{2+} during POST (6.7%) and RECOVERY (3.4%), but similar to K^+ these changes were not significant. None of the athletes displayed Mg^{2+} levels outside of the normal range (Table 5.3) during any measurement period.

Anions

There was no significant change in HCO_3^- levels in comparison to PRE during POST and RECOVERY. Three athletes displayed below normal HCO_3^- levels during PRE (probably as a result of their continual training during the investigation), which was reversed by the event and returned in two of the athletes after 24-48 hr of recovery. Chloride concentration was significantly decreased as a result of the triathlon (6.7%), and then returned to baseline levels after RECOVERY (Table 5.3). One athlete had an abnormally high Cl^- level (114 mmol/L) during PRE, which was normalized only after recovery from the triathlon. Four other athletes displayed a below normal Cl^- level POST, which was normalized in three of the four athletes after RECOVERY.

Anion Gap

The mean AG calculated as $[(Na^+ + K^+) - (HCO_3^- + Cl^-)]$ was significantly elevated (27.2%) POST and returned to baseline values after RECOVERY (Table 5.3). One athlete displayed an AG (25 mmol/L) above the normal limits (Table 5.2) during PRE, primarily as a result of a marked reduction in HCO_3^- concentration (15 mmol/L) (as discussed earlier). All participants had an AG above the normal limits during POST, and only one athlete had an AG (21 mmol/L) above the normal limits during RECOVERY.

Creatinine and Urea

There was a significant increase in creatinine concentration (17.5%) immediately after the race, which returned to baseline values 24-48 hr after the race (Table 5.3). None of the athletes displayed a creatinine concentration beyond the normal range during any of the measurement periods.

Urea concentration was significantly increased (19.0%) as a result of the race and remained slightly (9.5%) but not significantly elevated during RECOVERY (Table 5.3). Three of the athletes had urea concentrations above the normal range during PRE, and seven of the athletes had above normal urea concentrations during POST and RECOVERY.

Relationship between endogenous catecholamines and electrolytes after the race

The catecholamines of interest were elevated immediately after exercise in comparison to the norm for resting conditions as a result of the exercise bout (Table 5.3). There was no significant correlation between any of the endogenous catecholamines (Table 5.3) and the measured electrolytes (Table 5.4).

DISCUSSION

This was an unique opportunity to examine the effects of the Half Ironman Triathlon on a series of haematological and biochemical parameters. The major observations were the following: 1) performance in the Half Ironman Triathlon results in significant reductions in [Hb], Hct and RBC count during recovery, 2) the physiological stress of Half Ironman Triathlon results in increased WBC and platelets immediately after the race and, 3) competition in a Half Ironman Triathlon does not result in significant alterations in serum levels of Na^+, K^+, and Mg^{2+}.

Haematologic Changes as a Result of the Half Ironman Triathlon

The measurement of Hb, Hct, MCV and RDW provides key information on the presence and type of anaemia (1). Lowered [Hb] and Hct are indicative of potential anaemia, but in athletes this may merely represent dilutional anaemia. A RDW above the normal limits may represent iron deficiency, vitamin B_{12} deficiency and folic acid deficiency (39) all of which have been associated with endurance training (30). A MCV value of less than 75 fl suggests iron deficiency anaemia (1). The combination of the measurements of RDW and MCV allows for the determination of iron deficiency anaemia. Iron deficiency anaemia is associated with an increased RDW and a lowered MCV. Although measures of serum iron, transferrin saturation and serum ferritin (commonly measured indices of iron deficiency) were not examined, the RDW and MCV indicate that iron deficient erythropoiesis probably did not exist in these athletes before or after the completion of a Half Ironman Triathlon. Therefore, iron deficiency anaemia likely does not explain the lowered Hct and [Hb] in our athletes after the performance of the Half Ironman Triathlon.

The reduction in [Hb] and Hct occurred with concomitant reductions in RBC, but no significant changes in MCV or MCHC occurred. Therefore, the reduction in [Hb] and Hct are most likely the result of a primary reduction in RBC count and not changes in MCV and MCHC (4). This may indicate that the prolonged exercise did not result in changed RBC size or cellular [Hb] (11).

Red blood cell haemolysis as a result of prolonged strenuous exercise is well documented (5, 29). O'Toole et al. (29) reported that nearly all triathletes experience intra-vascular haemolysis during races lasting 2 hr or longer, and that the magnitude of the haemolysis was directly related to race distance. The mechanism responsible for this finding is most likely related to mechanical trauma brought about by repetitive footstrikes during running (footstrike haemolysis) (5, 29) and/or GI blood loss (25). Several other hypotheses have been put forward to explain the RBC haemolysis observed after prolonged strenuous exercise, which include an increased renal pressure as a result of renal vasoconstriction during exercise (15), increased erythrocyte compression due to muscle contraction (35), and increased osmotic fragility of erythrocytes (29, 35).

The source of the resultant haemodilution observed in our athletes after 24-48 hr of recovery from the Half Ironman Triathlon cannot be directly determined from the data available. However, the customary haemoconcentration seen immediately after prolonged exercise (28, 40) owing to PV loss (11) and/or splenic emptying (18) was not observed in our athletes. This may be indicative of the maintenance of pre-race hydration levels or a true loss of RBC during the race. It is therefore safe to assume that the reduced RBC, Hb, and Hct seen during RECOVERY were likely the result of the combination of exercise-induced increases in PV and RBC haemolysis. The former explanation is likely a "functional pseudoanaemia" which is generally not detrimental to aerobic performance and may even improve performance (4, 6). Whereas, the latter may have a significant impact on aerobic performance (6). What proportion each of these factors plays in the observed exercise-induced haemodilution remains to be determined.

Electrolyte changes as a Result of the Half Ironman Triathlon

Electrolyte balance during prolonged exercise is very important for optimal endurance performance. We were primarily interested in the effects of prolonged, strenuous exercise on Mg^{2+}, K^+ and Na^+, since previous reports have indicated that the prolonged exercise may result in significant alterations in these minerals. There was a slight reduction in Mg^{2+} and K^+ immediately after the completion of the race, but with the exception of Cl^{-1}, there was no significant alteration in any of our measured minerals.

Magnesium is a major cation involved in a series of metabolic pathways that are challenged during exercise conditions (23, 31). Exercise may increase the demand for Mg^{2+} and/or increase Mg^{2+} losses, potentially leading to Mg^{2+} deficits that may lead to muscle weakness, neuromuscular dysfunction, and tetany, all of which can affect physical performance (20, 31). Our athletes did not appear to have any significant Mg^{2+} deficiency before or after the completion of the Half Ironman Triathlon. However, serum or plasma Mg^{2+} may be of limited value since only 1% of the total body Mg^{2+} may be present in extracellular fluid (2).

Overt signs and symptoms of hypomagnesia (i.e. hyperirritability, tetany, convulsions, and cardiac arrhythmias) may not manifest until the serum Mg^{2+} concentration has decreased below 0.5 mmol/L. None of our athletes displayed a serum Mg^{2+} concentration which approached 0.5 mmol/L. There was a slight, but non-significant, reduction (6.7%) in serum Mg^{2+} immediately post-race, which returned to near baseline levels (3.4% below PRE) after 24-48 hr of recovery from the event. This finding is similar to the observations of other investigators (8, 20, 36) who reported reduced serum or plasma levels of Mg^{2+} immediately after prolonged strenuous exercise.

Potassium, the major cation of the intracellular fluid, is released from muscle cells during exercise and is directly related to the exercise intensity (21, 37, 38). The rise in K^+ (hyperkalemia) is rapidly reversed after rest (21, 24, 37) and may even be associated with a lowering of K^+ levels to below control levels (hypokalemia) (21, 24, 37).

The exercise-induced hyperkalemia generally has no effect on athletes and may even be attenuated in highly conditioned athletes (17). However, exercise-induced hyperkalemia may potentially be associated with dangerous cardiotoxicity (17) and arrythmogenic events in individuals with underlying coronary artery disease (34, 38) and could explain some instances of sudden cardiac death in athletes (19). The post-exercise hypokalemia may also be associated with arrythmogenic events in individuals with underlying coronary artery disease (38).

A non-significant reduction of 20% in K^+ concentration was observed immediately after the race and remained (12%) 24-48 hr after recovery. The hypokalemia observed immediately after the race is generally thought to be due to a re-uptake of K^+ into the muscle after exercise (21, 37, 38). This finding may be the result of the continuation of catecholamine stimulation of the sarcolemma Na^+-K^+ ATPase without anaerobic metabolism or muscle ischemia (21, 38). In contrast, Struthers et al. (37) found that the rapid changes in K^+ after a squash game could not be accounted for by changes in plasma catecholamine levels, since pre-treatment with a β_2-antagonist had no significant effect on the hypokalemia observed after exercise. They postulated that the resultant reduction in plasma K^+ may be due to alterations in insulin. Although we did not find a significant relationship between individual endogenous catecholamine levels and K^+ levels after the race, we cannot rule out the importance of a catecholamine mediated reduction in K^+. As expected, the plasma levels of catecholamines were well above the normal resting values immediately after the race and most likely played a role in the re-uptake of K^+ into skeletal muscle. Further research into the relative roles insulin and catecholamines have on K^+ levels post-exercise is warranted.

Exercise-associated hyponatremia (serum Na^+ values less than 130 mmol/L) has been observed in some athletes after prolonged exercise (27). Noakes and coworkers (27) observed that hyponatremia is present in only 0.3% of athletes engaged in prolonged exercise, however, 9% of collapsed ultra-endurance athletes display hyponatremia. Hyponatremia may have potentially fatal complications as outlined by Noakes et al. (27), which include "grand mal seizures, respiratory arrest, acute respiratory distress syndrome, coma, increased intracranial pressure, pulmonary edema and hypotension." None of our athletes collapsed after the race or displayed serum Na^+ levels that approached 130 mmol/L. Further research into the presence of hyponatremia in collapsed runners after the Half Ironman Triathlon is warranted.

White Blood Cells and Platelets

We observed a transient increase in WBC count and platelets immediately after the completion of the Half Ironman Triathlon. Both findings are common after prolonged endurance events (3, 32) and likely represent a normal response to physiological stress.

Conclusions

These results indicate that reductions in Hct, and [Hb] seen after the completion of the Half Ironman Triathlon are the result of reductions in RBC and are not likely associated with iron deficiency. The reduced RBC may be the result of an increased PV and/or RBC destruction (12). A reduced erythropoiesis secondary to an increased 2,3-DPG (leading to an increased oxygen delivery) may also explain these findings (12, 13). However, the changes observed in this investigation occurred well before alterations in erythropoiesis could be identified. Therefore, the short-term change observed in RBC and

[Hb] indicate that RBC destruction and/or PV expansion likely predominated.

Competition in the Half Ironman Triathlon does not result in significant alterations in the minerals Na^+, K^+ and/or Mg^{2+} in the majority of triathletes. However, small reductions in K^+ and/or Mg^{2+} may occur as a result of this form of exercise. It remains to be determined what role alterations in these minerals play in the development of the collapsed athlete.

Table 5.1. Participant characteristics (Mean ± SD).

Measure	Triathletes
Age (yr)	32 ± 5
Weight (kg)	72 ± 13
Height (cm)	180 ± 5
Systolic blood pressure (mmHg)	128 ± 11
Diastolic blood pressure (mmHg)	78 ± 5
Racing Experience (yr)	9 ± 5
Races per year (n)	7 ± 6
Average hours of training (hours/week)	12 ± 3
Finishing time (hours:min)	5:01 ± 0:24

Table 5.2. Haematological data taken 48-72 hr before (PRE), immediately after (POST), and 24-48 hr after (RECOVERY) the completion of a Half Ironman Triathlon (Mean ± SD).

Haematologic Measure	Normal Range	PRE	POST	RECOVERY
[Hb] (g/L)	140 - 180	149 ± 6	146 ± 5	137 ± 5*
Hct (%)	40 - 50	44 ± 1	44 ± 1	40 ± 2*
RBC (x 10^{12}/L)	4.6 - 6.2	4.8 ± 0.3	4.7 ± 0.2	4.4 ± 0.2*
WBC (x 10^9/L)	4.5 - 11.0	6.9 ± 1.5	18.5 ± 4.4*	6.9 ± 1.2
MCV (fL)	80 - 96	91.2 ± 2.4	91.2 ± 3.0	90.8 ± 2.5
MCHC (%)	32 - 36	33.7 ± 0.4	33.7 ± 0.4	33.8 ± 0.6
MCH (pg)	26 - 34	30.8 ± 0.8	30.8 ± 0.8	30.8 ± 1.0
RDW (%)	11.5 - 14.5	12.5 ± 0.5	12.4 ± 0.4	12.5 ± 0.4
Platelets (x 10^9/L)	150 - 350	188 ± 32	209 ± 27*	185 ± 32

[Hb], haemoglobin concentration, *Hct*, haematocrit; *RBC*, red blood cell count; *WBC*, white blood cell count; *MCV*, mean corpuscular volume; *MCHC*, mean corpuscular haemoglobin concentration; *MCH*, mean corpuscular haemoglobin; *RDW*, red blood cell distribution width; *PRE*, resting control condition; *POST*, measures taken immediately (15 to 30 min) after the event; *RECOVERY*, measures were taken after a period of recovery (24 to 48 hr) from the event; * significantly different from all other conditions, $p < 0.05$.

Table 5.3. Biochemical data taken 48-72 hr before (PRE), immediately after (POST), and 24-48 hr after (RECOVERY) the completion of a Half Ironman Triathlon (Mean ± SD).

Biochemical Measure	Normal Range	PRE	POST	RECOVERY
Sodium (mmol/L)	136 - 142	140 ± 3	140 ± 3	141 ± 1
Potassium (mmol/L)	3.5 - 5.1	4.1 ± 0.9	3.3 ± 0.3	3.6 ± 0.3
Magnesium (mmol/L)	0.65 - 1.05	0.89 ± 0.05	0.83 ± 0.09	0.86 ± 0.04
Chloride (mmol/L)	98 - 106	104 ± 4	97 ± 2*	104 ± 1
Bicarbonate (mmol/L)	22 - 29	21.4 ± 3.7	22.5 ± 1.8	23.8 ± 1.7
AG (mmol/L)	10 - 20	18.4 ± 3.6	23.4 ± 1.9*	17.6 ± 1.7
Creatinine (μmol/L)	53 - 106	97 ± 8	114 ± 8*	97 ± 9
Urea (mmol/L)	2.5 - 6.4	6.3 ± 1.1	7.5 ± 1.2*	6.9 ± 1.2
Norepinephrine (nmol/L)	0.38 - 1.89	–	4.17 ± 1.30	–
Epinephrine (pmol/L)	< 360	–	522.7 ± 280.8	–
Dopamine (pmol/L)	< 650	–	337.3 ± 145.8	–

AG, anion gap; *PRE,* resting control condition; *POST*, measures taken immediately (15 to 30 min) after the event; *RECOVERY,* measures were taken after a period of recovery (24 to 48 hr) from the event; * significantly different from all other conditions, $p < 0.05$; –, measures not taken.

Table 5.4. Relationship between endogenous catecholamines and electrolytes.

Catecholamine	Electrolyte				
	Sodium	**Potassium**	**Magnesium**	**Chloride**	**Bicarbonate**
Norepinephrine	$r^2 = 0.07$	$r^2 = 0.02$	$r^2 = 0.01$	$r^2 = 0.07$	$r^2 = 0.16$
	$p = 0.50$	$p = 0.72$	$p = 0.76$	$p = 0.48$	$p = 0.33$
Epinephrine	$r^2 = 0.06$	$r^2 = 0.27$	$r^2 = 0.00$	$r^2 = 0.11$	$r^2 = 0.02$
	$p = 0.52$	$p = 0.18$	$p = 1.00$	$p = 0.38$	$p = .75$
Dopamine	$r^2 = 0.12$	$r^2 = 0.14$	$r^2 = 0.18$	$r^2 = 0.16$	$r^2 = 0.00$
	$p = 0.37$	$p = 0.35$	$p = 0.25$	$p = 0.29$	$p = 0.89$

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CHAPTER SIX

Effects of Half Ironman Competition on the Development of Late Potentials in Triathletes

Abstract

Objectives: *The primary aim of this investigation was to evaluate the prevalence of late potentials (LPs) in healthy triathletes before and after a Half Ironman Triathlon. Secondly, we sought to examine whether LPs are the electrocardiographic expression of greater myocardial mass. Thirdly, we endeavoured to examine the literature regarding the prevalence of LPs in healthy individuals and the relationship between left ventricular mass and signal-averaged electrocardiogram (SAECG) parameters.* ***Methods:*** *Nine asymptomatic male triathletes (Mean Age ± SD 32 ± 5 years) were examined using SAECG 48-72 hours before (PRE), immediately after (POST), and 24-48 hours after the completion (RECOVERY) of a Half Ironman Triathlon. Late potentials existed if two of the following SAECG anomalies were observed: 1) a prolonged filtered QRS (fQRS) complex, 2) a lengthened low amplitude signal (LAS) duration, and/or 3) a low root mean square (RMS) voltage at a filter of 40-250 Hz. Left ventricular dimensions were determined at PRE using M-mode echocardiography.* ***Results:*** *There was no significant difference between PRE, POST, and RECOVERY in the fQRS duration (101.7 ± 10.8 ms, 101.9 ± 9.5 ms, 101.8 ± 9.7 ms, respectively), the LAS duration (29.8 ± 8.0 ms, 29.9 ± 8.6 ms, 29.9 ± 8.0 ms, respectively) or the RMS voltage (52.1 ± 32.0 μV, 44.3 ± 21.4 μV, 47.5 ± 32.8 μV, respectively). Two athletes displayed a single SAECG anomaly associated with LPs during PRE and two SAECG anomalies (i.e., LPs) during POST. Late potentials remained in one of the two athletes, who previously displayed SAECG anomalies during RECOVERY. A moderate relationship existed between fQRS and left ventricular mass ($r=0.67$, $p < 0.05$).* ***Conclusions:*** *Ultra-endurance training and/or events do not lead to LPs in the majority of athletes who do not possess ventricular arrhythmias. However, a small subset of triathletes may display SAECG anomalies associated with LPs, which are augmented by an ultra-endurance event and may persist even after recovery from the event. The significance of LPs in this athletic population remains to be determined. Left ventricular mass does not affect SAECG parameters.*

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INTRODUCTION

Physical activity has long been shown to result in beneficial adaptations to the cardiovascular system and provide long-term health benefits. However, recent evidence indicates that repeated bouts of prolonged, strenuous exercise may lead to deleterious effects on the myocardium. This is evident by the recent trend wherein a relatively high proportion of highly trained ultra-endurance athletes have been shown to develop impaired left ventricular systolic function after prolonged strenuous exercise (6, 25). The mechanism behind this occurrence has yet to be elucidated. It has been postulated that the myocardium, which was once thought to be fatigue resistant, fatigues as a result of prolonged, strenuous exercise (6, 14). It is possible that the fatigued heart may impair performance at best or result in sudden cardiac death (SCD) at worst.

The risk of SCD during prolonged strenuous exercise is well documented (18, 20, 28) dating as far back as 500 BC, when the legendary Pheidippides, collapsed and died after running from Marathon to Athens. Sudden cardiac death in young competitive athletes (less than 35 years of age) most commonly occurs in the setting of hypertrophic cardiomyopathy, whereas in athletes older than 35 years the most common cause of SCD is coronary artery disease (10, 16). However, the incidence of SCD following exercise is really low (10,16).

An alarming statistic is that only 25% of those athletes who die suddenly are diagnosed before participation in strenuous exercise (17). Currently, a number of noninvasive techniques, such as ECG stress testing and echocardiograpy are utilized for the detection of those individuals at risk of SCD (10). The widespread use of these procedures is not economically feasible and therefore many athletes at risk for SCD may never be diagnosed.

Signal-averaged electrocardiography (SAECG) is effective in the determination of late potentials (LPs) and may be useful for the detection of problems associated with cardiac fatigue in athletes. Late potentials are low-amplitude signals at the terminal portion of the QRS complex and within the ST segment (15, 27). These low potential signals are manifestations of myocardial zones with delayed and non-uniform activation that represent potential sites for the development of re-entrant ventricular arrhythmias and SCD (3, 9, 15, 27).

The most common use of SAECG is for the prediction of LPs in post-myocardial infarction patients (9, 13, 26). Recent research has looked at the usefulness of SAECG detection of LPs in athletes who perform prolonged strenuous exercise (1, 27). Smith and coworkers (27) revealed that marathon running may improve SAECG parameters. However, no investigation has examined the effects of training and/or competition in the Half Ironman Triathlon on SAECG parameters. Therefore, the primary purpose of this investigation was to assess the prevalence of LPs in triathletes before and after completing a competitive ultra-endurance Half Ironman Triathlon.

It has also been postulated that abnormal SAECG parameters in healthy adults are the electrocardiographic expression of a greater myocardial mass (22). Thus, prolonged training which results in an increased LV mass may be associated with an increased risk for the development of ventricular arrhythmias during prolonged exercise. Therefore, the secondary purpose was to determine if any relationship exists between the presence of LPs and left ventricular mass. The final purpose was to compare our results to the few investigations, which examined SAECG parameters in athletes and normally active participants during resting conditions and/or after strenuous exercise.

METHODS

Athletes

Nine healthy male triathletes (Age 32 ± 5 years; Height 180 ± 5 cm; Weight 75 ± 11 kg) were selected for this investigation based on the entrance criteria of a predicted completion time of five hours or less. Exclusion criteria for these athletes included the following: 1) any known myocardial disease, 2) presence of risk factors for coronary artery disease, 3) family history of SCD at a young age, and 4) uninterpretable ECG, such as bundle branch block. Baseline clinical characteristics of the participants are listed in Table 6.1. Subjects participated in regimented training programs in preparation for triathlon competitions training on average 12 hours/week (Table 6.1). The event was a standard Half Ironman Triathlon, with a 2 km swim, a 90 km bike and a 21 km run.

Signal-averaged Electrocardiogram

Signal-averaged electrocardiograms were conducted on all athletes after careful placement of electrodes in the three bipolar X, Y, and Z orthogonal lead system as previously described (3, 15). Signals were acquired using the Arrhythmia Research Technologies Inc. Model 1200EPX Acquisition module (Austin, TX). Each recording consisted of an average of at least 250 beats with an acceptable noise level of ≤0.2 μV. Each recording was downloaded to a MS-DOS compatible personal computer and analysed using Arrhythmia Research Technologies Inc. Time Domain Analysis Software Version 4.0. A Bidirectional Butterworth Filter with a bandpass of 40 to 250 Hz was used. Start and end points of the filtered QRS (*f*QRS) were automatically determined by the computer to eliminate operator variability and bias. All SAECG measures were conducted by the same operator to eliminate inter-observer variability.

Baseline measures of SAECG in all athletes were taken 48-72 hr before (PRE) and 24-48 hr after (RECOVERY) the triathlon. Measures of SAECG in all athletes were also conducted 2-3 hr after completion of the triathlon (POST). All measures were taken in the supine position. Late potentials were considered to be present if the athletes demonstrated two of the following time-domain SAECG criterion: 1) a *f*QRS complex of ≥114 ms, 2) a low amplitude signal duration under 40 μV (LAS) > 38 ms, and/or 3) root mean square voltage of the last 40 ms (RMS) < 20 μV (9). Further support of abnormal SAECG was given by three-dimensional spectral temporal analysis. A "normality factor" of < 30% in any one of the X, Y, or Z leads was considered to be abnormal and used to quantify differences between participants (15).

Echocardiographic Measurements

The left ventricle was imaged only at PRE with a Hewlett-Packard ultrasound instrument (Sonos 5500, Hewlett-Packard, Massachusetts) with a 3.5 MHz transducer and recorded in the left lateral decubitus position during quiet respiration. Left ventricular morphology was examined using the parasternal short axis view. M-mode measurements of LV internal dimension in diastole, LV internal dimension in systole, ventricular septal wall thickness, and posterior wall thickness were made in accordance with the American

Society of Echocardiography guidelines (24). Left ventricular mass was estimated according to the corrected American Society of Echocardiography formula (5).

STATISTICS

Changes in the time-domain SAECG parameters of interest (*f*QRS, LAS, RMS) and the normality factors from the spectral temporal analysis were evaluated using repeated measures (three levels) one-way analysis of variance (ANOVA). The level of significance was set a priori at $p < 0.05$. The relationship between SAECG parameters and left ventricular mass was determined via linear regression.

RESULTS

Time Domain Analysis

Baseline SAECG data were obtained from all nine participants during all test periods. Signal-averaged ECG findings from all three test periods are reported in Table 6.2 and Figure 6.1. There was no significant difference in the *f*QRS duration between PRE, POST and RECOVERY (Table 6.2)(Figure 6.1). There was also no significant difference between PRE, POST, and RECOVERY in the LAS signal duration or the RMS voltage (Table 6.2)(Figure 6.1).

A total of eight SAECG anomalies were observed in the group of athletes during all three time periods. Two athletes (Table 6.2) displayed a single SAECG anomaly associated with LPs during PRE, but none displayed two or more SAECG anomalies (i.e., no LPs). However, the same athletes did display LPs (two out of three SAECG anomalies) 2-3 hours after the triathlon. Late potentials only remained during RECOVERY in one of the two athletes who previously displayed SAECG anomalies.

Spectral Temporal Mapping

Three-dimensional analysis of multiple segments within the QRS complex and the ST segment allowed for further analysis of the SAECG. No significant differences existed in the normality factors of each testing period as illustrated in Figure 6.2. However, the use of spectral temporal analysis confirmed the presence of high-frequency activity in the terminal portion of the signal-averaged QRS complex and the beginning of the ST segment at POST and RECOVERY in one subject who displayed time domain abnormalities and in one subject at PRE who did not display time domain abnormalities (Table 6.2).

Relationship between SAECG parameters and echocardiographic measures

Baseline left ventricular mass data were obtained from eight of the nine participants during PRE. Linear regression analysis revealed that left ventricular mass was moderately correlated to *f*QRS ($r=0.67$, $p < 0.05$) (Figure 6.3). Also, weak correlations between left ventricular mass and LAS and RMS existed ($r=0.38$, $r=-0.43$, respectively, $p > 0.05$).

DISCUSSION

To the best of our knowledge, this investigation is the first to examine the effects of prolonged, strenuous exercise on the development of LPs in healthy asymptomatic triathletes. Although the endurance event did not significantly affect the SAECG parameters of interest in the group as a whole, a small subset of the athletes did experience SAECG anomalies associated with LP as a result of their training and/or the exercise itself. Therefore, the major findings of this investigation are that: a) ultra-endurance training and/or events do not lead to LPs in the majority of asymptomatic athletes, b) a small subset of athletes (two out of nine) do display SAECG anomalies pre-competition, which are worsened by the event itself, c) one athlete (out of nine) displayed LPs after 48-72 hr of recovery from a Half Ironman Triathlon and d) a prolonged *f*QRS duration is associated with an increased left ventricular mass.

Few investigations have examined the prevalence of LPs using SAECG in athletes and/or healthy subjects (Table 5.3) (1, 2, 4, 12, 19, 23, 27). Our results are comparable, with our athletes displaying mean SAECG parameters of a similar magnitude to the mean values reported by investigators reviewed in Table 5.3 (*f*QRS = 102 ms versus 99 ms, LAS = 30 ms versus 27 ms, RMS = 52 ms versus 51 ms, respectively). These investigations also revealed a very low prevalence of abnormal SAECG parameters in healthy participants (0-10%) (4, 22) and athletes (0-9%) at rest (1, 2, 19, 27). Similarly, our investigation revealed that none of our athletes displayed the standard requirements of two out of three SAECG anomalies at PRE. However, two out of nine did display a single SAECG anomaly associated with LP during PRE.

Biffi and coworkers (1) reported that LPs are not found in healthy athletes without arrhythmias, whereas 28% of athletes with ventricular arrhythmias displayed LPs during resting conditions. Biffi et al. (1), however, used a stringent SAECG criterion for the classification of LPs (three out of three anomalies). Using the standard requirement of two out of three anomalies, one (3%) of their athletes displayed LPs, whereas one athlete (3%) displayed a single SAECG anomaly associated with LPs. This finding was supported by a subsequent investigation from the same laboratory (2) and by the results of the present investigation.

Only one investigation has examined the prevalence of LPs in athletes before and after a prolonged endurance event (27). Smith et al. (27) examined the effects of marathon running on SAECG parameters and reported that marathon running actually improved SAECG parameters. However, of interest was the finding that one marathoner (3%) displayed at least two of three abnormal SAECG parameters (thereby meeting our criteria for the presence of LPs) before the marathon run. This abnormal SAECG was normalized immediately after the marathon run and returned between seven and 14 days after the race. Interestingly, another runner who did not exhibit SAECG abnormalities before and immediately after the marathon, demonstrated LPs after seven to 14 days of recovery. Taken with the results of the present investigation, this may indicate that ultra-endurance events increase the likelihood of the development of LPs in some endurance athletes. The development of these LPs may be detectable using SAECG, however, only after suitable recovery from the activity. This hypothesis will require further investigation with a much larger sample size.

Smith and coworkers (27) postulated that the absence of abnormal SAECG and the actual improvement in the SAECG parameters seen immediately after the marathon may represent the effects increased heart rate and/or changes in the autonomic nervous system resulting from the event. Smith et al. (27) acquired SAECG approximately 20 min (16.7 ± 12.4 min) after the race, whereas we measured SAECG on our athletes 2-3 hours after the completion of the triathlon. It is possible that by initiating the SAECG data acquisition later, we were able to avoid the effects of exercise-induced changes in heart rate and autonomic nervous system, thereby allowing for a clearer assessment of the effects of prolonged exercise on the development of LPs. Thus, exercise may actually improve SAECG parameters and the SAECG may be of little use in the prediction of LPs when administered immediately after a race. However, the predictive value of SAECG may be more impressive when used before a race or after recovery from an endurance event.

The majority of investigations reporting cardiac fatigue in athletes have examined ventricular function after an ultra-endurance event. For example, a series of investigations by Douglas and coworkers (6-8) assessed the effects of ultra-endurance events on left ventricular function in athletes competing in the Hawaii Ironman Triathlon (2.4 mile swim, 112 mile bicycle ride, and a 26.2 mile run). They reported that left ventricular systolic function was significantly reduced as a result of the Ironman triathlon. The athletes in this investigation also displayed a depressed systolic function post-marathon (11). Smith et al. (27) postulated that LPs may occur in these athletes as a result of "more extreme events," such as the Half and Full Ironman triathlons. This is supported by the data of our experiment and may indicate that the duration and/or type of an event may have an impact on the development of cardiac fatigue and LPs.

Raineri et al.(22) postulated that abnormal SAECG parameters may be the electrocardiographic representation of a greater myocardial mass. Raineri and coworkers (23) reported a significant correlation between the signal-averaged QRS duration and body size, particularly body height, in normal subjects. In a subsequent investigation (22), they postulated that a prolonged *f*QRS may be related to left ventricular mass (22). These authors reported a significant relationship between the signal-averaged QRS duration and left ventricular mass (r = 0.60), with weak correlations between left ventricular mass and LAS and RMS (r = 0.30, r = -0.26, respectively). They postulated that a prolonged *f*QRS may not only represent non-homogeneous and delayed myocardial electrical activity, but is also the electrographic expression of an elevated left ventricular mass. Our results compare quite well to that of Raineri and coworkers in that *f*QRS duration was moderately related to left ventricular mass (r = 0.67), with weak correlations between left ventricular mass and LAS and RMS (r = 0.38, r = -0.43, respectively). The physiological significance of the finding is however debatable. For instance, in our investigation the two athletes who displayed prolonged *f*QRS durations, both had LV dimensions and masses within normal limits (21).

This is supported by two investigations by Biffi (1) and coworkers who despite finding a moderate correlation between *f*QRS duration and left ventricular mass in healthy athletes reported that left ventricular mass did not seem to affect the *f*QRS duration for values greater than 114 ms. They concluded that physiological hypertrophy does not alter SAECG parameters. Therefore, left ventricular mass did not seem to significantly affect overall SAECG parameters.

Another interesting finding was revealed by Moroe et al. (19) who examined 796 athletes using SAECG and found that those who engage in continuous anaerobic exercise experience a greater occurrence of abnormal SAECG. They postulated that continuous anaerobic exercise may result in delayed or non-homogeneous myocardial conduction. What effect the different exercise modalities (swimming, bicycling and running) have on the utilization of the anaerobic system and the development of SAECG abnormalities during the triathlon is unclear and requires further investigation.

The presence of LPs in two out of nine athletes after an ultra-endurance event may indicate that prolonged, strenuous exercise may result in electrical instability within the myocardium of athletes who perform these activities. However, as to whether these athletes may be at increased risk for the development of ventricular tachycardia and possibly SCD is unknown. As the incidence of SCD in athletes is very low, much larger investigations would be required to determine if the presence of LPs at rest of after strenuous exercise is associated with increased risk of SCD in asymptomatic, healthy endurance athletes.

Table 6.1. Participant characteristics (Mean ± SD).

Measure	Triathletes
Age (yr)	32 ± 5
Weight (kg)	75 ± 11
Height (cm)	180 ± 5
Systolic blood pressure (mmHg)	128 ± 11
Diastolic blood pressure (mmHg)	78 ± 5
Racing Experience (yr)	9 ± 5
Races per year (n)	7 ± 6
Average hours of training (hours/week)	12 ± 3
Finishing time (hours:min)	5:01 ± 0:24

Table 6.2: Signal-averaged electrocardiogram parameters before and after a Half Ironman Triathlon in asymptomatic athletes ($\bar{x} \pm SD$).

Variable	PRE	POST	RECOVERY
*f*QRS (ms)	101.7 ± 10.8	101.9 ± 9.5	101.8 ± 9.7
LAS(ms)	29.8 ± 8.0	29.9 ± 8.6	29.9 ± 8.0
RMS (μV)	52.1 ± 32.0	44.3 ± 21.4	47.5 ± 32.8
*f*QRS ≥ 114 ms	1	1	0
LAS > 38 ms	1	2	1
RMS < 20 μV	0	1	1
1 criterion	2	0	0
2 criterion	0	2	1
3 criterion	0	0	0
Athletes with LPs	0	2	1
Normality Factor <30%	1	1	1

fQRS, filtered QRS; *LAS*; low amplitude signal duration under 40 μV; *RMS*, root mean square voltage of the last 40 ms; *LPs*, late potentials.

Table 6.3. Average signal-averaged electrocardiogram and echocardiographic data reported in the literature for normal participants and athletes.

Investigation (Reference)	n	Age	G	C	Signal Averaged ECG			Echocardiographic Data					
					*f*QRS (ms)	LAS (ms)	RMS (ms)	LVIDd (mm)	LVIDs (mm)	VST (mm)	PWT (mm)	FS (%)	LVM (g)
Present Investigation	9	32	M	TRI	102	30	52	53	31	10	10	41	202
Biffi (1)	3525	2525	M M	ISO ISO*	99110	2240	5925	- -	- -	- -	- -	- -	- -
Denes (4)	30	26	M/F	N	96	24	67	-	-	-	-	-	-
Jordaens (12)	1510 15	2625 25	M M M	CYC BB N	1e+07	3e+05	4e+05	555753	363835	11129	12119	3333 33	3e+08
Moroe (19)	796	19	M/F	COM	101	26	57	51	32	9	9	37	195
Raineri (23)	3328	4138	M F	N N	9892	3134	3630	- -	- -	- -	- -	- -	- -
Raineri (22)	71	39	M/F	N	95	31	37	-	-	-	-	-	146
Smith (27)	30	37	M/F	MAR	97	23	60	54	34	-	-	36	212

n, number of participants; *G*, gender (*M*, male or *F*, female); *C*, participant classification (*CYC*, cyclists; *BB*, basketball players; *N*, normal; *TRI*, triathletes; *ISO*, athletes were selected from aerobic-isotonic sports; *MAR*, marathon runners); *fQRS*, filtered QRS; *LAS*, low amplitude signal duration under 40 μV; *RMS*, root mean square voltage of the last 40 ms; *LVIDd*, left ventricular internal dimension in diastole; *LVIDs*, left ventricular internal dimension in systole; *VST*, intraventricular septal wall thickness; *PWT*, posterior wall thickness; *FS*, fractional shortening; *LVM*, left ventricular mass; *, group of athletes with frequent and complex ventricular arrhythmias; – , data not available.

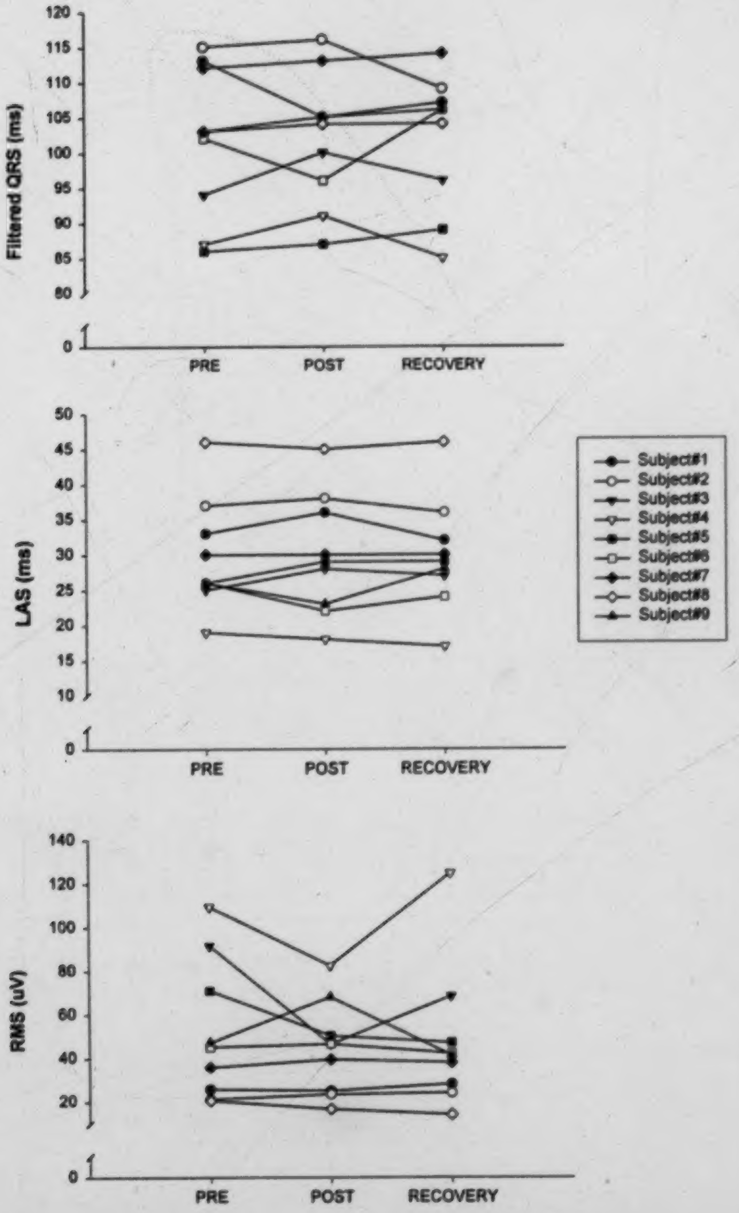

Figure 6.1. Effects of the Half Ironman Triathlon on signal-averaged electrocardiogram parameters. Measures were taken 48-72 hr before (PRE), 2-3 hr after (POST) and 24-48 hr after (RECOVERY) the Half Ironman Triathlon.

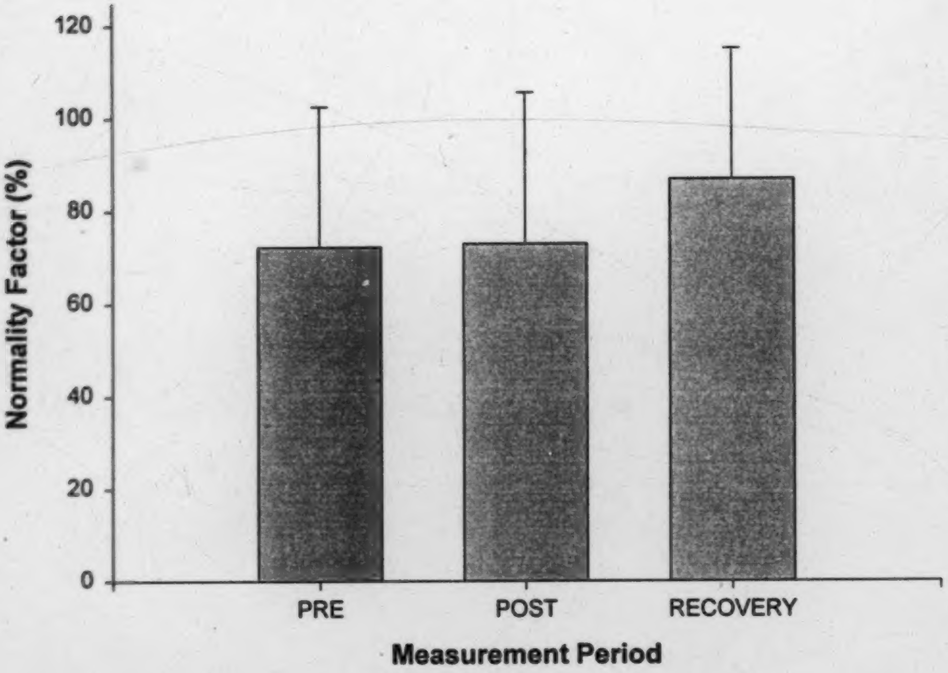

Figure 6.2. The effects of the Half Ironman Triathlon on normality factors (Error Bars = SD). Measures were taken 48-72 hr before (PRE), 2-3 hr after (POST) and 24-48 hr after (RECOVERY) the Half Ironman Triathlon.

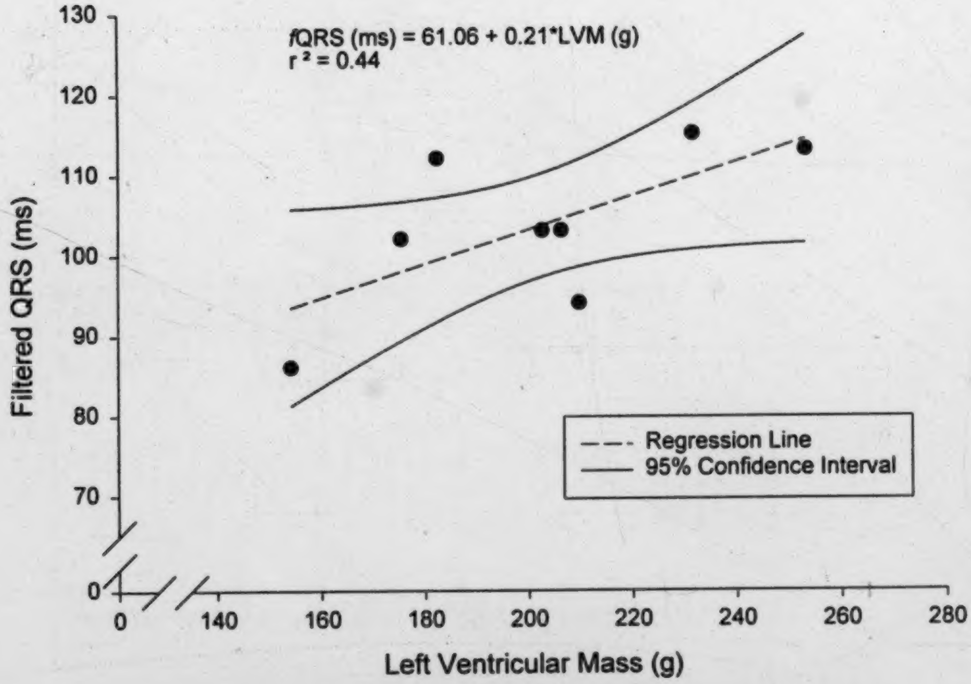

Figure 6.3. Relationship between left ventricular mass and filtered QRS duration. Measures taken in eight participants.

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CHAPTER SEVEN

SUMMARY

The enhanced cardiovascular function of endurance athletes: What is the mechanism of primary importance and how can this knowledge be applied to other populations?

SUMMARY

Endurance training has been associated with several central and peripheral adaptations including an increased stroke volume (SV), cardiac output ($\dot{Q}$), arterio-venous oxygen difference (a-$\bar{v}DO_2$) and maximal aerobic power ($\dot{V}O_2$max). Improvements in cardiac function as evaluated by $\dot{Q}$ and SV have been shown to account for a large portion of the enhanced cardiovascular function after training. However, the mechanisms of improvement remain unclear. Increases in SV are related to a series of factors including heart size, myocardial contractility, and venous return (3).

There is considerable debate as to the SV response to incremental exercise before and after training. Several investigators have postulated that at low and moderate exercise intensities, the Frank-Starling mechanism is responsible for the increase in SV and $\dot{Q}$ (14, 18, 35). Whereas, during the later stages of vigorous exercise $\dot{Q}$ is increased through the exercise-induced increases in heart rate and myocardial contractility. Stroke volume is thought to reach a plateau at approximately 40% of $\dot{V}O_2$max, owing to a limitation in the time for diastolic filling (14, 21, 35). This finding is believed to be consistent in both trained and untrained individuals.

However, other investigators have postulated that highly trained endurance athletes make use of the Frank-Starling mechanism throughout incremental to maximal exercise (8, 15, 16, 25, 51, 52, 56). The increased capacity for utilizing the Frank-Starling mechanism was thought to be the result of an enhancement in ventricular filling, owing in part to the elevated blood volume (BV) of the endurance athletes (15, 25).

The results presented in Chapter Three of this manuscript revealed that endurance-trained individuals do in fact make use of the Frank-Starling mechanism throughout incremental to maximal exercise in both the supine and upright positions. However, the relative contribution of the Frank-Starling mechanism to the increase in SV and $\dot{Q}$ during exercise is markedly affected by postural position. In the supine and upright positions, SV continues to increase throughout incremental exercise as a result of increases in end-diastolic volume (EDV) and myocardial contractility. Significant differences in SV, however, are only seen up to a heart rate of approximately 110 beats·min^{-1}. Also, the magnitude of changes in SV are significantly different between the upright and supine positions. Upright exercise is associated with a significantly greater elevation in SV and a greater reliance on the Frank-Starling mechanism throughout incremental to maximal exercise in comparison to supine exercise. It is possible that the increased venous return (i.e., EDV) brought about by the supine position places these athletes closer to the limits of their diastolic reserve than the upright position. The pericardium may ultimately limit the magnitude of changes seen in SV and EDV in the supine and upright positions. Previous work in this area tends to be confounded by differences in postural position, testing procedures, measurement techniques and/or participant fitness levels.

Also, of importance was the finding that with an acute change in venous return (brought about by a shift from the upright to supine positions) there was a significant improvement in diastolic function. This supports previous research which indicates that acute changes in BV have a large impact on diastolic function in normally active and endurance-trained individuals (15-17, 25, 49, 51).

A large portion of the enhanced cardiovascular function of endurance-trained athletes has been associated with their high BV (15-17, 25). Endurance-trained individuals generally have a BV which is approximately 15% larger than their non-trained counterparts (as reviewed in Chapter Two). Increases in BV are associated with concomitant enhancements in SV, $\dot{Q}$ and $\dot{V}O_2$max (15-17, 25, 49, 51). However, debate exists regarding the independent role BV plays in the enhanced cardiovascular function of endurance-trained athletes (24, 50).

Given the potential importance of BV on cardiovascular function, maximizing the gains in BV may be of benefit for optimizing aerobic performance. Based on the review of the literature (as discussed in Chapter Two) there is a direct relationship between the duration of training (irrespective of frequency and intensity) and the elevations in BV. Therefore, it holds that continuous training at a moderate intensity may lead to greater improvements in BV in comparison to interval training. If BV plays a role in the determination of $\dot{V}O_2$max, it is also conceivable that continuous training would result in a significantly larger increase in $\dot{V}O_2$max.

Also, of interest is the role a series of hormones involved in BV regulation have on the induction and maintenance of BV expansion following different forms of endurance training. Previous findings are equivocal regarding the impact of endurance training on resting concentrations of volume-regulatory hormones. Also, no investigation has directly addressed the differential effects of continuous or interval training on hormones involved in volume regulation.

Finally, endurance training is commonly associated with increased LV dimensions (13, 34). Left ventricular hypertrophy resulting from endurance training is generally thought to be the result of a chronic volume overload (13). As such, training which augments BV and $\dot{Q}$ has the potential for increasing LV dimensions. Whether or not continuous training results in a greater increase in LV morphology than interval training remains unclear?

The investigation presented in Chapter Four addresses the impact of different forms of endurance training on BV, hormones involved in BV regulation, and LV morphology and function. This investigation has revealed that continuous training results in a significantly greater improvement in vascular volumes (i.e., PV and BV) in comparison to interval training. A small, but insignificant, improvement in $\dot{V}O_2$max was seen after continuous training in comparison to interval training. This seemed to be related to the impact of differences in BV and $\dot{Q}$ between training groups. The changes in vascular volumes resulting from both training programs accounted for a large portion of the enhancement in $\dot{V}O_2$max. Therefore, these results give further support that the training-induced BV expansion plays a large role in the enhanced cardiovascular function of endurance-trained individuals.

Also, of interest was the finding that the participants were able to make greater use of the Frank-Starling mechanism after training. However, despite the increased capacity to utilize the Frank-Starling mechanism after training, the participants still used myocardial contractility and tachycardia to increase their $\dot{Q}$ during the later stages of vigorous exercise. Therefore, short-term training does not seem to elicit the same myocardial adaptations as seen with chronic training (as discussed above). Also, twelve weeks of aerobic training does not result in the same magnitude of BV expansion as seen in cross-sectional investigations. This may indicate that short term training does not provide a sufficient stimulus to increase BV or myocardial function to the levels seen after chronic training. These results may also indicate that there is a genetic component to BV and myocardial function, such that those individuals with the largest BV and/or largest myocardial capacity are self-selected into endurance activities.

Training had little impact on resting concentrations of aldosterone and atrial natriuretic peptide, which is a consistent finding in the literature (48). However, the early increases in vascular volumes were associated with a significant elevation in angiotensin II. This may indicate that the early increases in vascular volumes are related to changes in the renin-angiotensin system. However, the resting concentration and total amount of angiotensin II decreased to baseline levels after one week of training, despite the maintenance of an elevated BV. Therefore, it would appear that the changes in the volume-regulatory hormones only account for a small portion of the training-induced BV expansion.

Twelve weeks of continuous or interval aerobic training also did not result in a significant change in LV morphology. This is common after short-term training (19, 37) and may indicate that 12 weeks of aerobic training provides an insufficient stimulus for LV morphological adaptations. Thus, significant changes in cardiovascular fitness and left ventricular function can occur without changes in LV morphology. Also, the increased heart size observed commonly in endurance-trained cyclists in cross-sectional comparisons may be the result of their prolonged training or due to their genetic makeup, self-selection to endurance events, and/or the non-training environment.

As evaluated in Chapters One, Two and Three endurance training results in several cardiovascular adaptations that are of benefit for both performance- and health-related fitness. However, recent research has revealed that prolonged exercise may take normally active and trained individuals alike to the limits of their physical performance. Several investigations have revealed that prolonged strenuous exercise (generally continuous exercise for more than two hours) may lead to a decrement in several key factors involved with performance (2, 9, 10, 12, 20, 26, 31-33, 36, 38, 40, 44, 54, 55). Given the impact vascular volumes have on performance it is important to understand the effects of prolonged exercise on vascular volumes and their determinants. Also, other investigators have revealed that serious complications (potentially fatal) may arise from changes in electrolytes (32). Serious electrolyte imbalances may occur from hyperhydration with hypotonic solutions ("water intoxication") (32) or excessive loss of electrolytes through sweat during exercise.

Athletes commonly display an impaired LV systolic function after prolonged strenuous exercise (9, 20, 31, 40). It is possible that a small proportion of these athletes display a delayed electrical activation of the myocardium as a result of their training (2, 54), which is worsened by the event itself (54). The delayed activation of the myocardium (as evaluated by signal-averaged ECG) has also been associated with an increased LV mass. Therefore, it is possible that prolonged training which results in an increase in LV mass may result in an increased risk for the development of ventricular arrhythmias.

With the potentially serious complications (from both a performance- and health-related point of view) arising from prolonged strenuous exercise it is important to develop a clearer understanding of the maladaptations that may occur during these events. The results presented in Chapter Five indicate that prolonged strenuous exercise results in significant alterations in vascular volumes and/or related haematologic indices. These changes may serve to decrease the potential for optimal performance, but are of minimal concern from a health-related point of view. Prolonged strenuous exercise in the form of the Half Ironman Triathlon does not result in significant alterations in several important electrolytes including sodium, potassium and magnesium. As long as electrolyte balance is maintained, serious complications associated with electrolyte imbalances are unlikely to occur.

Chapter Six indicates that ultraendurance training and/or events generally do not result in a delayed electrical activation of the myocardium in the majority of asymptomatic athletes. However, a small subset of athletes display electro physiological anomalies, which are augmented by prolonged exercise and remain even after recovery. However, whether these individuals are at an increased risk for the development of ventricular arrhythmias and/or sudden death remains to be determined. Also, there is a positive relationship between LV mass and electro physiological anomalies. However, the physiological significance of this finding seems minimal.

Applying this Knowledge to Patients with Cardiovascular Disease

In recent years there has been wide spread experimental support for the benefits of exercise training for the rehabilitation of patients with cardiovascular disease (4, 6, 7, 28, 30, 39, 41, 43). Exercise rehabilitation has been shown to be effective for several patient populations including congestive heart failure patients, patients who suffered a myocardial infarction, patients who underwent coronary bypass or heart valve surgery, and patients who received a heart transplant (6). Rehabilitation has been associated with several positive outcomes including reduced morbidity, increased exercise tolerance, improved lipid-lipoprotein profiles, improved psychological well-being and improved quality of life (6, 28, 41). It has also been postulated that mortality rates will be reduced in this population after cardiac rehabilitation (28, 41). However, experimental data supporting this hypothesis is lacking (28, 41).

The majority of longitudinal training investigations in patients with cardiovascular disease have examined the effects of continuous training corresponding to 40 to 85% of $\dot{V}O_2$max. As outlined above, these training regimes have been shown to result in several beneficial adaptations in patients with cardiovascular disease. However, this form of training may also result in significant cardiac strain, owing to exercising for prolonged periods of time at high SV and $\dot{Q}$. The exercise-induced BV expansion may also result in an increased myocardial stress. The increased myocardial stress may result in a series of myocardial morphologic (i.e., chronic volume overload-induced increases in left ventricular (LV) dimensions and mass) and functional adaptations. These adaptations are generally thought to be of benefit for healthy individuals and patients with cardiovascular disease. However, in certain populations where the ventricle is already overloaded and fully utilizing the Frank-Starling mechanism (e.g., congestive heart failure (CHF)), these adaptations may be of concern.

Congestive Heart Failure

Congestive heart failure is a multi-factorial disease, which is commonly associated with left ventricular (LV) dysfunction (28). The prevalence of CHF has doubled in the past 30 years with approximately 250,000 Canadians having CHF (47). The depressed cardiac function of CHF patients (i.e., reduced ejection fraction) is associated with high rates of morbidity and mortality. The average life expectancy of

CHF patients is 4 to 5 years and is predominantly due to the continuance of the depressed cardiac function and sudden death (22, 27, 28). The hallmark of CHF is fatigue and dyspnea, which leads to a reduced exercise capacity and a decreased ability to perform daily activities and thus a resultant poor quality of life.

Recent evidence has revealed that the symptoms of CHF (e.g., congested liver, engorged neck veins, pulmonary rales) are the result of two major problems: 1) volume overload, and 2) reduced exercise capacity associated with breathlessness and fatigue. As outlined in Figure 7.1 the symptoms of CHF are not simply due to a reduction in myocardial function (5), but a combination of factors which leads to a vicious cycle of decline.

Severe diastolic dysfunction is a common feature of CHF (5, 41) and is associated with several abnormalities including 1) an elevated pulmonary artery wedge pressure (filling pressure) with no change in EDV, 2) a reduced SV and $\dot{Q}$, 3) pericardial constraint (owing to volume overload and/or pulmonary congestion), 4) myocardial hypertrophy (owing to volume overload, which is further exacerbated by mitral regurgitation), 5) mitral regurgitation (owing to the fact that the valves can no longer cover the orifices of the hypertrophied heart) and 6) β_1-downregulation (5, 41, 45). As a result of the reduction in LV function, CHF patients generally become inactive and have a reduction in muscle perfusion (Figure 7.1). The former is the result of a reduced exercise capacity, but may also be related to the doctor recommendations for minimal activity (as discussed later).

Similar to deconditioning, CHF results in a series of events which lead to muscle wasting and minimize the effectiveness of oxidative metabolism, thereby increasing the dependence on glycolysis to meet the demands of everyday living (45). Congestive heart failure also results in a series of pulmonary abnormalities including 1) decreased lung compliance (owing to pulmonary congestion and perhaps fibrosis), 2) increased ventilation (as a result of increased acidosis, increased dead space, and/or over-stimulated ergoreceptors), 3) pulmonary edema, 4) decreased perfusion of the respiratory muscles (leading to early respiratory muscle fatigue due to reduced oxygen delivery), and 5) increased dead space-to-tidal volume ratio (leading to further ventilation-perfusion inequities) (5, 41, 45).

Vascular abnormalities are also associated with the inactivity and decreased muscle perfusion. Vascular abnormalities commonly observed in CHF patients include increased systemic vascular resistance and increased vascular tone (5, 41, 45). These may be the result of the a reduction in vasodilatory metabolite production, and/or a reduced endothelial release off relaxing factors, such as nitric oxide. An overstimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone systems is a common finding in CHF. It has been postulated that the ergoreceptors that are responsive to chemical stimuli sense the lower metabolism, leading to an overactivation of the sympathetic nervous system (5).

The result of these abnormalities is a further worsening of the volume overload. The reduction in muscle perfusion will decrease the blood flow to the kidneys. In response to a decreased renal perfusion (as in exercise) there will be an increased stimulation of the renal sympathetic nerves and an increased release of anti-diuretic hormones (i.e., renin, angiotensin II, aldosterone, vasopressin). This will serve to increase vascular tone, increase the retention of water and electrolytes and reduce diuresis (decreased urine outflow), such that arterial pressure is normalized. Thus, fluid homeostasis is sacrificed to maintain circulatory perfusion pressures. The net effect is an increase in ventricular preload on an already overloaded heart, which leads to a vicious cycle (as illustrated in Figure 7.1).

Congestive heart failure patients have generally been advised to avoid physical activity with the underlying fear that physical activity will lead to a further deterioration of their cardiac function (28). However, recent investigations have shown that exercise training may improve the impaired exercise capacity and reduce the symptoms of CHF (1, 28, 46). Improvements in exercise capacity may reduce the rates of morbidity and mortality as well as improve the patients' quality of life (28).

Therefore, aerobic training has a significant impact on the overall health status of patients with CHF. However, the exact mode of aerobic exercise to be used to achieve the greatest benefits requires further investigation. Currently, most investigations assessing exercise training on cardio-respiratory fitness in CHF patients have used the conventional rehabilitation training model of continuous exercise training (as outlined above). In healthy individuals, this form of training has been shown to result in improvements in SV, $\dot{Q}$, and $\dot{V}O_2$max. Coincident with this improved cardiovascular function is an expanded BV and a potential for increases in LV morphology.

However, this form of training may not be the most suited for CHF patients, where improvements in VO_2max are desired, but changes in BV and LV morphology (i.e., chronic volume overload) are not. We postulated that interval training would lead to similar improvements in VO_2max, but would not enhance BV to the same extent as seen with continuous training. Therefore, the morphologic adaptations associated with continuous training and BV expansion may be minimised with interval training.

However, a paucity of information exists regarding the alterations in BV, and myocardial morphology and function that occur as a result of interval training. The investigation presented in Chapter Four has shown that interval training results in similar improvements in $\dot{V}O_2$max with smaller changes in BV. Thus, interval training may be more appropriate for those individuals with cardiovascular disease, especially congestive heart failure patients, where improvements in aerobic fitness are desirable, but alterations in LV morphology and increases in BV are not. Also, given the potential for peripheral adaptations resulting from interval training (as discussed in Chapter Four) the peripheral maladaptations associated with CHF may be affected to a greater extent by training that utilizes a high intensity stimuli (29). Further research is required to evaluate this hypothesis, since the present investigation did not find significant peripheral adaptations.

There is currently no research examining the chronic effects of prolonged interval training on BV, and LV morphology and function in patients with underlying cardiovascular disease. Based on the findings of the present dissertation, a prospective, randomized, multi-centre trial (i.e., University of British Columbia, University of Alberta, and McMaster University) has been proposed to examine the impact of interval training and continuous training on patients with cardiovascular disease. We have postulated that the benefits of aerobic training in CHF patients will be optimized through the use of interval training.

It is important to note that the interval training utilized in this investigation resulted in a significant improvement in BV. Thus, interval training, although seemingly more appropriate for CHF patients than continuous training, may not be appropriate for those CHF patients with severe volume overload. Resistance training has recently gained widespread acceptance for patients with cardiovascular disease (53). Although resistance training has little impact on the central determinants of $\dot{V}O_2max$ (53), CHF patients commonly have peripheral limitations (as outlined above) which may be improved upon by resistance training. Future studies should look at the effects of resistance training on patients with CHF.

Patients with cardiovascular disease commonly display delayed or non-homogeneous activation of the myocardium (11). In fact, the most common use of the signal-averaged ECG is in the prediction of late potentials in post-myocardial infarction patients (11, 23, 42). The incidence of late potentials in patients with cardiovascular disease is markedly higher than that observed in normally active or endurance-trained individuals. Based on the findings reported in this manuscript, it holds that prolonged exercise (i.e., greater than 5 hours of continuous exercise) may be associated with an increased risk for the development of ventricular arrhythmias or sudden death. Future research is required to evaluate this hypothesis.

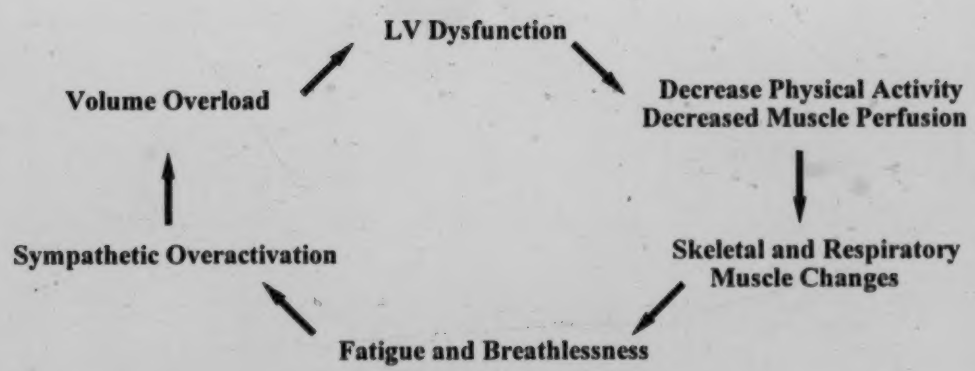
LV Dysfunction
Decrease Physical Activity
Decreased Muscle Perfusion
Skeletal and Respiratory Muscle Changes
Fatigue and Breathlessness
Sympathetic Overactivation
Volume Overload

Figure 7.1. Vicious cycle of decline observed in congestive heart failure.

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Appendix A

Determination of Oxygen Uptake

Oxygen uptake ($\dot{V}O_2$) is the amount of oxygen consumed per minute ($L \cdot min^{-1}$) and can be determined using an open circuit technique. Oxygen consumption is equal to the amount of oxygen inspired ($\dot{V}_IO_2$) and the amount of oxygen expired ($\dot{V}_EO_2$):

$$\dot{V}O_2 = \dot{V}_IO_2 - \dot{V}_EO_2, \text{ and}$$

$$\dot{V}_IO_2 = \dot{V}_I \cdot F_IO_2,$$

where, F_IO_2 = the fractional concentration of inspired oxygen (i.e., 0.2093), and

$$\dot{V}_EO_2 = \dot{V}_E \cdot F_EO_2,$$

where, F_EO_2 = the fractional concentration of expired oxygen as determined by gas analysis

Therefore, $$\dot{V}O_2 = (\dot{V}_I)(F_IO_2) - (\dot{V}_E)(F_EO_2)$$

Only $\dot{V}_I$ needs to be calculated to determine $\dot{V}O_2$, since F_IO_2, $\dot{V}_E$, and F_EO_2 are either known or measured.

To calculate $\dot{V}_I$ we use the Haldane transformation, which is based on the fact that nitrogen is physiologically inert and as such the volume of nitrogen ($\dot{V}_IN_2$) is equal to the volume of nitrogen expired ($\dot{V}_EN_2$).

Therefore, $\dot{V}_I \cdot F_IN_2 = \dot{V}_E \cdot F_EN_2$, can be simplified to:

$$\dot{V}_I = (\dot{V}_E \cdot F_EN_2) / F_IN_2$$

where, F_IN_2 = fractional concentration of nitrogen in inspired air (i.e., 0.7904)
F_EN_2 = fractional concentration of nitrogen in expired air as measured by gas analysis

Since inspired air is comprised of nitrogen (0.7904), oxygen (0.2093), and carbon dioxide (0.0003), we can calculate F_IN_2 and F_EN_2 from:

$$1 = F_IN_2 + F_ICO_2 + F_IN_2$$

or

$$F_IN_2 = 1 - (F_IO_2 + F_ICO_2)$$

and

$$F_EN_2 = 1 - (F_EO_2 + F_ECO_2)$$

Therefore, $\dot{V}_I = (\dot{V}_E) \cdot [1 - (F_EO_2 + F_ECO_2)]/[1 - (F_IO_2 + F_ICO_2)]$

Both F_EO_2 and F_ECO_2 can be determined from the gas analysis, allowing $\dot{V}_I$ to be calculated. Oxygen uptake can then be calculated as follows:

$$\dot{V}O_2 = (\dot{V}_E \cdot F_EN_2/F_IN_2 \cdot F_IO_2) - (\dot{V}_E \cdot F_EO_2)$$

Oxygen uptake is expressed either in absolute ($L \cdot min^{-1}$) or relative ($mL \cdot kg^{-1} \cdot min^{-1}$) terms.

Appendix B

Determination of Plasma Volume and Blood Volume

Plasma volume, measured by the Evans Blue dye technique, is calculated according to the following equation:

$$PV = (20\ k/D) \cdot F$$

where,

D = optical density of dyed plasma sample at 610 nm
k = constant of dye lot

where,

$$k = D/C$$

D = optical density of the standard at 610 nm
C = concentration of standard (0.004 $mg \cdot mL^{-1}$)
F = correction factor based on the amount of dye injected for each subject (i.e., 0.75 = 15 mg dye injected; 1.00 = 20 mg dye injected)

The volume of dye injected is dependent on the subject's body weight: 15 mg (3 mL) is used for participants weighing between 100 and 180 lbs, while 20 mg (4 mL) is used for participants weighing greater than 180 lbs.

Blood volume can be calculated from the following formula:

$$BV = PV/(100 - Hct(corr))$$

where,

$Hct(corr) = Hct \cdot 0.91$, in which, 0.91 = venous to whole body haematocrit ratio.

Appendix C

Radioimmunoassay Procedure for α-Atrial Natriuretic Peptide and Angiotensin II

These procedures are based on the manufacturer's instructions supplied with the radioimmunoassay (RIA) kits (Phoenix Pharmaceuticals, California).

Extraction of the Peptide from Plasma

The use of unextracted plasma for the determination of α-atrial natriuretic peptide or angiotensin II has been shown to result in inconsistent results. Therefore, extraction procedures are generally used to separate the peptide of interest from the plasma. These procedures are termed Solid-Phase extraction and are based on the principles of liquid chromatography, with slightly different applications. Liquid chromatography allows for the continuous interaction of the sample with the sorbent bed as it flows through the column. Differences in structure allow the various constituents of the sample to exit the column at different times. As such, separation and collection at different times allow for the measurement of the components of interest. With Solid-Phase Extraction, the first phase of the protocol is such that there is complete retention of the sample peptide, while the interfering compounds are washed away. A solvent is then applied to the column that causes complete "elution" (removal) of the peptide from the sorbent bed, where it is collected for further analysis. The extraction procedure used in the removal of α-atrial natriuretic peptide or angiotensin II involved the following steps:

1. One mL of plasma was acidified with 1 mL of 1% trifluoroacetic acid (TFA, HPLC Grade) in water (Buffer A, RK-BA-1, Phoenix Pharmaceuticals, California). This mixture was vortexed and centrifuged at 3000 revs·min^{-1} for 15 min at 4°C.
2. A SEP-COLUMN containing 200 mg of C_{18} (RK-SEPCOL-1) was equilibrated by washing with 1 ml of buffer B followed by buffer A (3 mL, 3 times). Twenty-one SEP-COLUMNS (per extraction procedure) were attached to a multi-port vacuum manifold and a light vacuum pressure was applied to the columns to allow a flow rate of 1 to 5 L·min^{-1} (this was applied during each phase of the extraction).
3. The acidified plasma solution was loaded onto the equilibrated C_{18} SEP-COLUMN and the plasma was slowly drawn through the column with a light vacuum pressure.
4. The column was then washed twice with 3 mL of buffer A to remove any weakly retained-compounds. The waste wash was collected into polystyrene tubes and then transferred to microcentrifuge tubes. The microcentrifuge tubes were frozen at -80°C as a fail safe, in case the extraction procedures were not successful.

5. The peptide contained within the extraction column was slowly eluted with buffer B (3 mL, once) and the eluent was collected into a polystyrene tube.
6. The eluent was evaporated to dryness using a speed vacuum and lyophilizer. The lyophilization equipment consisted of a speed vacuum centrifuge (Speed Vac® Sc 110-120, Savant Instruments Inc., Farmingdale, N.Y.) attached to a freeze dryer (Labconco® Freeze Dryer 4.5,) and a vacuum pump (Precision Vacuum Pump, Model DD 195, Precision Scientific Inc., Chicago, ILL.).
7. The lyophilized peptide was reconstituted in 250 μL of RIA buffer on the day of the RIA procedure.

Radioimmunoassay Procedure

1. Eight standard reaction mixtures (in duplicate) were created with 500 μL of a known concentration of the standard peptide mixed with 500 μL of the RIA buffer for the creation of a "standard curve" (ranging from 1-128 pg per tube).
2. Three sets of duplicate tubes were created for the determination of total counts (TC), non-specific binding (NSB), and total binding (TB). Duplicate polystyrene tubes were also labelled for each of the samples.
3. The reconstituted samples were aliquoted into the duplicate polystyrene tubes (100 μL per tube).
4. Each tube (except the TC and NSB) received 100 μL of the primary antibody (rabbit anti-peptide serum, reconstituted in 13 mL of RIA buffer). The NSB tubes received 200 μL of the RIA buffer. All tubes were vortexed and incubated in for 24 hours at 4°C.
5. The ^{125}I-peptide supplied by the manufacturer was reconstituted with 13 mL of the RIA buffer and vortexed. The concentration of this tracer solution was then evaluated to ensure that the level of radioactivity was sufficient for the assay (e.g., 8,000 to 10,000 counts·min^{-1}·100 μL).
6. Every tube received 100 μL of this tracer solution, vortexed, and then incubated for 24 hours at 4°C.
7. The goat anti-rabbit IgG serum (GAR) and normal rabbit serum (NRS) were reconstituted with 13.0 mL of the RIA buffer, respectively.
8. Each tube (except the TC tubes) received 100 μL of both GAR and NRS, were vortexed, and incubated at room temperature for 90 min.
9. Each tube (except the TC tubes) received 500 μL of the RIA buffer, and were vortexed.
10. All tubes were centrifuged (except the TC tubes) at 3000 revs·min^{-1} for 20 min at 4°C.
11. The supernatant was aspirated (except the TC tubes) to separate the bound and unbound peptides. The radioactivity of the remaining pellet was then assessed using a gamma camera and compared against the standard curve to determine the concentration of the unknown samples.
12. The amount of the peptide in the original sample was determined by multiplying the concentration of the assayed sample by the dilution factor used in the preparation of the sample (i.e., 1 mL to 0.25 mL = 2.5 correction factor).

Appendix D

Radioimmunoassay Procedure for the Measurement of Aldosterone

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The RIA procedure for the measurement of aldosterone was performed on unextracted serum using Coat-A-Count procedures. Polypropylene tubes already coated with antibodies specific to aldosterone were supplied by the manufacturer along with seven aldosterone calibrators (i.e., lyophilized human serum containing 0 to 1,200 pg of aldosterone per mL after reconstitution) and ^{125}I-aldosterone. In addition, the supplier provided a tri-level human serum-based immunoassay control, which contained aldosterone as one of its components. Two controls with known concentrations were utilized to ensure accurate readings on the RIA kit. The RIA procedure was as follows:

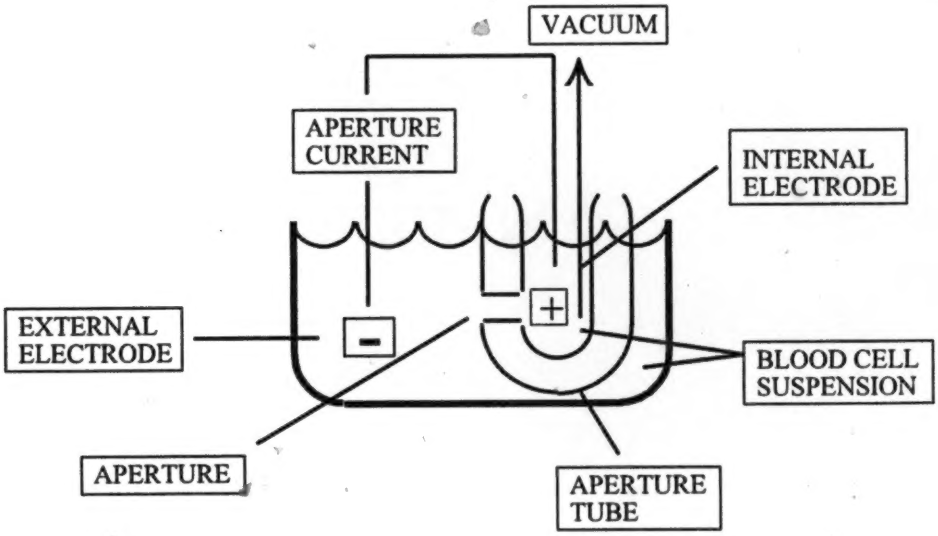
1. Duplicate plain (uncoated) 12 x75 mm polypropylene tubes were labelled for total counts (TC) and non-specific binding (NSB).
2. 200 μL of each calibrator was pipetted into corresponding labelled tubes to allow for the construction of a "standard curve" (ranging from 0 to 1,200 pg$\cdot$mL^{-1}). The NSB tubes received 200 μL of the zero calibrator (which contained no aldosterone).
3. 200 μL of the control and patient serum was injected into the prepared duplicate tubes. The TC tubes only received the ^{125}I-aldosterone.
4. Every tube received 1.0 mL of the ^{125}I-aldosterone and was vortexed gently.
5. The samples were allowed to incubate overnight for 18 hours at 4°C.
6. The supernatant was aspirated (except the TC tubes) to separate the bound and unbound peptides. The radioactivity remaining bound to the coated tubes was then determined using a gamma camera and compared against the standard curve to determine the concentration of the unknown samples.

Appendix E

Coulter Blood Counting Procedures

Coulter Principle

The Coulter principle is an electronic method for counting and sizing particles by measuring changes in electrical resistance as cells suspended in a conductive liquid (diluent) pass through a small aperture via a delicate vacuum (diagram). An electrical current is passed between two submerged electrodes (internal and external). The internal electrode is located withing the aperture housing and the external electrode is suspended in the aperture bath (cell dilution). As an individual cell passes through the aperture, it increases the resistance to flow of the electrical current. The change in resistance is recorded as a pulse that can be counted and sized. Total cell count is determined by the number of pulses and the size of each cell is determined by the amplitude of the electrical pulse.


VACUUM
APERTURE CURRENT
INTERNAL ELECTRODE
EXTERNAL ELECTRODE
-
+
BLOOD CELL SUSPENSION
APERTURE
APERTURE TUBE